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Genetic predispositions to atopic eczema and psoriasis: survey, meta-analyses and comparison

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1. Introduction

Atopic eczema and psoriasis are two of the most common disorders affecting the skin. They are classified among the chronic inflammatory skin diseases together with allergic contact dermatitis and rosacea. Their high prevalence all over the world, their growing impact on health care systems and their substantial influence on the quality of life are only a few reasons why a lot of research has been done on both atopic eczema and psoriasis over the past decades.

A number of study groups tried to unravel the causes looking for genetic and environmental factors, while others aimed to understand the disease mechanisms and the contributing factors. Yet others observed the clinical course in order to formulate diagnostic criteria or to classify the diseases according to severity, age of onset or laboratory parameters. In addition, epidemiological data was collected from different countries and ethnicities.

In order to gain an overview, the most striking research results on atopic eczema and psoriasis shall be summarized in the following. The said results specify the diseases according to clinical, histological and epidemiological features as well as their pathogenesis and etiology. Subsequently, the separate specifications of atopic eczema and psoriasis will be compared to each other. Similarities shall give an insight of why a shared background of atopic eczema and psoriasis is suspected.

1.1. Specification of atopic eczema

As mentioned, atopic eczema is a very common disease which can lead to an significant impairment of social life. Due to its chronic course with long-term therapy costs, it poses a heavy burden not only on the single patient but on the society generally [532]. Since 1980, a huge number of publications dealt with different aspects of the said skin disease. Relevant studies include investigations on clinical characteristics trying to find diagnostic criteria, epidemiological analyses concerning disease prevalence in different populations and frequent updates on the pathogenesis. These help to give a comprehensive picture of atopic eczema.

1.1.1. Clinical, histological and epidemiological features of atopic eczema

Atopic eczema is known under a number of different names, among them atopic dermatitis, prurigo Besnier, infantile eczema, endogenous eczema or just eczema. Especially the

terms atopic dermatitis and atopic eczema are often used synonymously [1]. It is common knowledge that the disease affects the skin and takes a chronic course. This description, however, is not sufficient to characterize it properly. As no specific laboratory parameter is available to objectively confirm a suspected diagnosis, diagnostic features have to be based on clinical findings. This is important to rule out differential diagnoses including fungal infections like tinea capitis and tinea corporis, infestations like head lice and scabies or other skin conditions like guttate psoriasis. [355]

In 1980, Hanifin and Rajka established diagnostic guidelines for atopic eczema. They described basic features and minor features depending on symptoms, morphology, distribution, clinical course and history. The examined case has to present at least three out of four basic features and three out of 23 minor features to make a formal diagnosis of atopic eczema. To obtain the said features it is mandatory to take an exact medical history and to perform a physical examination. In the following, the disease characteristics forming the four basic features are listed. [166]

1. Pruritus
2. Lichenification
    - flexor involvement in adults or
    - facial and extensor involvement in infants and children
3. Chronically relapsing course
4. Atopic history
    - personal or
    - family members

Some examples for the 23 less characteristic minor features are xerosis, elevated serum IgE, early age of onset, tendency toward cutaneous infections as well as a Dennie-Morgan infraorbital fold. To get a correct diagnosis of atopic eczema the outlined diagnostic criteria by Hanifin and Rajka, including basic features and minor features, remain widely accepted and used. [166]

This is justified, inter alia, by the outcome of a statistical analysis which was performed more than two decades after the establishment of the criteria. At that time De et al 2006 [109] found a sensitivity of 96%, a specificity of 93.75%, a positive predictive value of 97% and a negative predictive value of 91.84% for Hanifin and Rajka's criteria in 101 paediatric patients with atopic eczema and 48 controls from Northern India. By this they showed a statistical advantage over the UK working party's diagnostic criteria which include features like itchy skin, dry skin, visible flexural dermatitis, history of flexural dermatitis, history of atopy and onset under the age of 2 years (P value < 0.005).

The histological aspect of acute eczematous lesions is dominated by an epidermal intercellular edema, the so-called spongiosis. Around capillaries there is a characteristic

[1] For clarity the term *atopic eczema* will be used hereafter.

inflammatory infiltrate consisting of dendritic cells, macrophages, monocytes, lymphocytes and eosinophiles. Chronic lesions on the contrary, show a thickened epidermis together with a hypertrophy of the upper layer. [39]

While the aspect of eczematous patches concedes the diagnosis of atopic eczema, the extent of the disease can vary strongly. All manifestations from limited and mild through moderate to generalized and severe are possible. Especially severe forms can lead to sleep disturbances which affect the performance at school and the quality of life in general [448]. In clinical trials, the Scoring Atopic Dermatitis Index (SCORAD) is used to assess the disease severity. It includes objective features like extent and intensity of lesions as well as subjective symptoms like daytime pruritus and sleep loss. [260]

Atopic eczema shows an early onset of symptoms, passing through different stages. It is usually diagnosed in infancy during the first six months of life [448] and possibly persists until adulthood due to its chronically relapsing course. According to age and distribution of lichenification, atopic eczema can be divided into three sequential phases. [448]

1. Infantile phase
    - from birth
    - involvement of cheeks, forehead and scalp
    - erythematous papules and vesicles
2. Childhood phase
    - from two years
    - involvement of hands, feet, wrists, ankles, antecubital and popliteal regions
    - lichenified papules and plaques
3. Adult phase
    - from puberty
    - involvement of flexural folds, face, neck, upper arms, back, dorsa of hands, feet, fingers and toes
    - dry scaling erythematous papules and plaques as well as large lichenified plaques

Depending on IgE levels, atopic eczema was formerly divided into two subgroups. True atopic eczema was classified as the "allergic" or "extrinsic" form showing elevated total serum IgE levels. "Nonatopic" eczema, in contrast, was formerly called the "non-allergic" or "intrinsic" form indicated by normal IgE levels [44]. The latter was found to be less frequent affecting only 10-30% of all patients [525]. Consequently, a differing pathogenesis was suspected with "extrinsic" eczema being closer to the pathogenesis of atopic diseases like asthma and allergic rhinitis which are characterized by elevated IgE levels as well [44]. Nowadays however, "nonatopic" eczema is considered as a transient phase in the natural history of the disease [39].

In terms of related disorders, atopic eczema is the most frequent initial manifestation of the atopic march leading to an increased risk of developing allergic rhinitis or asthma. In addition, children with atopic eczema show an elevated frequency of cutaneous infections. Especially *staphylococcus aureus*, *herpes simplex* and *molluscum contagiosum* are very common. [448]

Concerning epidemiology, Williams et al 1999 [527] conducted a worldwide study on the prevalence of atopic eczema. Their data comprised 256,410 children aged 6 to 7 years from 90 centers and 458,623 children aged 13 to 14 years from 153 centers in 56 countries all over the world. They found that there was a slight dependency on sex, preferring females over males ($1.3 : 1.0$). The highest prevalences of characteristic disease symptoms were found in Northern Europe and Australia, lower ones in Eastern and Central Europe and Asia. Prevalences reached from less than 1% to over 17% between countries and even within countries there was a wide variation, proposing environmental factors for disease expression. [527]

Especially decreasing exposure to pathogens during infancy is a popular idea to explain an increasing incidence of atopic eczema over the past decades. The so-called "hygiene hypothesis" implies that a poor stimulation of the immune system in early life could promote the development of eczema. Accordingly, the following factors have shown to reduce the eczema risk: day-care attendance, pets and more than one sibling. [526]

1.1.2. Pathogenesis and etiology of atopic eczema

To the pathogenesis of atopic eczema there are two different views. The "inside-outside"-hypothesis claims that the primary cause of the disease is a immunologic dysregulation which causes Ig-mediated sensitization and local inflammation leading to an epithelial barrier dysfunction in turn. In contrast, the "outside-inside"-hypothesis states that a defect in the epithelial barrier is essential for the immunologic effects to occur. [39]

In either of these two ways, both a dysfunction of the skin barrier and a deviation of the immune response seem to be involved in the development of atopic eczema. Bieber 2008 [39] provided a detailed outline of the mechanisms of disease, taking all relevant research results on the topic into consideration. The key aspects of this review article shall be summarized in the following paragraphs.

A reason why the skin barrier dysfunction could be primary to the inflammation are the current findings on the structural protein filaggrin. It seems to play a more significant role than other proteins like involucrin and loricrin or the lipid composition of the epidermis. Filaggrin forms part of the keratin cytoskeleton in epithelial cells and its degradation products are essential for water-binding in the epithelium. Consequently, a malfunction results in both an increased transepidermal allergen penetration due to the disturbed barrier function and a larger water loss. One way in which the efficiency of this protein can be negatively affected are genetic variants in the FLG gene. A modified expression of the FLG gene by underlying inflammation, however, is another way to impair the protein function.

The skin inflammation in atopic eczema involves epithelial cells like keratinocytes. These produce proinflammatory cytokines as well as chemokines in order to recruit

T cells to the skin. Such a keratinocyte activity is induced by distinct mechanisms. On the one hand mechanical irritative signals provoked by scratching could stimulate keratinocytes to secrete said mediators. On the other hand T cells reacting (IgE-independent) to allergens on the skin or in food could cause a keratinocyte response. Both of them are non-IgE-mediated mechanisms.

In the natural history of the disease, an IgE-mediated allergic sensitization does not necessarily occur. Sensitization to allergens in food and/or the environment happens weeks or months after the appearance of the first eczematous lesions in 60-80% of patients, which show a special genetic predisposition and an influence by *staphylococcus aureus* enterotoxin products. An additional sensitization to self-proteins is witnessed in approximately 25% of adult patients. This may be caused by scratching as released intracellular proteins are able to mimic allergen-derived epitopes and trigger an IgE response (molecular mimicry).

As a consequence, atopic eczema seems to go through different stages. First, there is a nonatopic eczema before any kind of sensitization occurs. Second, IgE-mediated allergen sensitization is induced by genetic factors, transforming the nonatopic form into true atopic eczema. Third, intracellular proteins released by scratching can act as autoantigens inducing an IgE response and turning the disease into an autoallergic atopic eczema.

The epidermal barrier dysfunction makes it easier for allergens with a high molecular wight to penetrate the skin. Especially molecules in pollens and food allergens are able to activate dendritic cells which in their turn differentiate naive T cells into effector cells. Hereby, interleukin-12 and interleukin-18 lead to the production of Th1 cells and interleukin-4 to the production of Th2 cells. Th1 cells in turn produce interferon-γ and interleukin-5, Th2 cells on the contrary interleukin-4, interleukin-5 and interleukin-13. Only interleukin-31 is secreted by both cell types.

If there are no polarizing signals by interleukins, Th0 cells are created in response and turn out both Th1 and Th2 products. Under normal conditions there would be a balance between the different types of helper T cells. In atopic eczema, however, an imbalance towards Th2 cells leads to an allergic condition with IgE overproduction due to B cell activation mediated by interleukin-4, interleukin-5 and interleukin-13 secreted by the Th2 cells.

Allergens penetrating through the barrier defect are not the only ones to stimulate dendritic cells to drive Th2 polarization. Interleukin-7-like thymic stromal lymphopoietin (TSLP), cytokines and chemokines produced by keratinocytes in atopic skin cause dendritic cells to secrete a special chemokine. This Th2-cell-attracting thymus- and activation-regulated chemokine (TARC/CCL17) in turn leads to Th2 cell production. Thus, local processes in the inflamed skin can cause a systemic reaction of the adaptive immune system and lead to a IgE-mediated sensitization.

The enhanced Th2 production represents the initial phase of skin inflammation in atopic eczema. The course of inflammation is biphasic, however, where the Th2 dominated acute phase is followed by a chronic phase with Th1 and Th0 cell dominance. In the acute phase a special population of myeloid dendritic cells, the so-called Langerhans' cells, play an important role. They express the high-affinity receptor (FCϵRI) in large

quantity and are activated when aeroallergens bind to the said receptor by the means of specific IgE. In response, they secrete interleukin-16 and monocyte chemotactic protein 1 (MCP-1) which lead to a migration of CD4+ T cells and monocytes into the skin.

The said monocytes subsequently differentiate into specialized myeloid dendritic cells, the so-called inflammatory dendritic epidermal cells (IDEC). These cells are responsible for two things. First, they enhance inflammation by secreting proinflammatory cytokines like TNF-α, interleukin-1 and interleukin-6. Second, they promote the switch from Th2 predominance to Th1/Th0 by secreting interleukin-12 and interleukin-18. By this, they induce the transition from the acute phase to the chronic phase of atopic eczema.

Regulatory T cells, expressing CD25 and FOXP3, show increased levels in patients suffering from atopic eczema. Yet their contribution to the disease is not yet clear.

The contribution of *staphylococcus aureus*, on the contrary, is well studied. A colonization of the akin can be witnessed in over 90% of patients with atopic eczema. The bacterium and its products induce further inflammation and sensitization by a variety of mechanisms. *Staphylococcus aureus*-derived ceramidase, for example, worsens the skin barrier defect leading to an increased permeability. Furthermore, its enterotoxins cause the production of enterotoxin-specific IgE initiating an IgE-mediated reaction against *staphylococcus aureus*.

Yet enterotoxins do not only lead to a direct antigen-independent T cell activation, but also to an augmentation of skin-homing receptor cutaneous lymphocyte-associated antigen (CLA) on T cells. By the up-regulation of keratinocyte-derived thymic stromal lymphopoietin (TSLP) and interleukin-31, the recruitment of T cells is further increased. In addition, T cells are manipulated in their response to local corticosteroid treatment by the induction of a competing isoform of the needed receptor, leading to corticosteroid resistance in T cells.

As mentioned, the presence of *staphylococcus aureus* leads to an up-regulation of interleukin-31 secreted by T cells. As this cytokine is pruritogenic and frequently found in atopic skin lesions, it seems to be a key factor for persistent pruritus as an important symptom of the disease.

In summary, Bieber 2008 [39] describes the pathogenesis of atopic eczema as an interplay between skin barrier function and immune system. The course of the disease can be divided into different phases according to sensitization on the one side and T cell activity on the other side. In the context of sensitization, there are three stages to be considered. First, there is a nonatopic stage if no kind of sensitization is detected. Second, there is a atopic stage if IgE-mediated allergen sensitization takes place. Third, there is a autoallergic stage if an additional sensitization to self-proteins occurs. In terms of T cell activity, one can distinguish between an acute phase and a chronic phase where Th2 predominance is followed by Th1/Th0 predominance. In addition, *staphylococcus aureus* and its products play an important role in the pathogenesis of atopic eczema.

However, time has passed since Bieber 2008 [39] completed his comprehensive review on disease mechanisms. As a consequence, an update was published by Novak and Bieber 2012 [345]. Above all, there were new findings on the T cell response. Besides Th2 and Th1/Th0 cells, further helper T cells like Th17 and Th22 seem to be involved. Their numbers are increased in lesional as well as non-lesional skin and both produce cytokines

playing an important role in the immune response and allergic reactions. While Th17 cells secrete interleukin-17, interleukin-21 and interleukin-22, Th22 cells are only capable of producing interleukin-22. Interestingly, interleukin-22 seems to impair the skin barrier function by its impact on keratinocytes. Acanthosis as well as a down-regulation of filaggrin and other important proteins of the epidermal differentiation complex (EDC) are observed. Still, the role of the additional types of helper T cells and their corresponding cytokines seems not completely clear yet. [345]

The etiology of atopic eczema is referred to as multifactorial or complex as both environmental and genetic factors contribute to its development. While the involvement of environmental factors was substantiated by a regionally varying prevalence within countries and an increasing incidence over the past decades, twin studies provided initial evidence of underlying genetic factors by showing higher concordance rates in monozygotic than in dizygotic twins [423, 365]. Since then, the genetic component of psoriasis has been intensively researched accumulating a large amount of data. An analysis of this data on genetic predispositions to atopic eczema forms the first part of this work.

1.2. Specification of psoriasis

Similar to atopic eczema, psoriasis is a very common disease causing a high morbidity rate worldwide. It impairs the quality of life substantially and influences the health economy by high long-term treatment costs and additional social costs [331]. The disease characteristics have been intensely researched over the past decades, involving studies on clinical and histological features as well as studies on epidemiological aspects. In addition, growing insight into the pathogenesis and etiology has been gained. This helps to characterize the disease more precisely.

1.2.1. Clinical, histological and epidemiological features of psoriasis

It is common knowledge that psoriasis is a chronic skin disease which can affect nails and joints. Unlike atopic eczema, there are no validated diagnostic criteria in the case of psoriasis. This is due to the fact that the diagnosis is usually straightforward if the lesions are seen by a specialist. Yet there are some borderline cases where the diagnosis is not as obvious. In order to adapt to these not uncommon cases Rzany et al 1998 [407] demanded the establishment of reliable diagnostic criteria. However, no such criteria have been implemented to date. As a consequence, the diagnosis does still rely on individual findings of specialists.

The common clinical presentations of psoriasis are sharply demarcated, erythematous, scaling plaques located on the scalp, in the intergluteal cleft, elbows or knees. In addition, nail changes like pitted nails or subungual hyperkeratosis are representative. The differential diagnoses of psoriasis include seborrhoeic dermatitis, lichen simplex chronicus, lichen planus, tinea corporis, subacute cutaneous lupus erythematosus, pityriasis rubra pilaris and Sezary's syndrome. [269]

In 2007, Griffiths and Barker published a detailed review on the clinical features of

psoriasis. They gave a comprehensive overview of the different clinical variants and their characteristics. In the following, the most important phenotypes are described in detail (according to Griffiths and Barker 2007 [158]).

Psoriasis vulgaris

alias: chronic plaque psoriasis

occurrence: 90% of all patients, commonest variant of psoriasis

distribution: symmetrically with extensor involvement of elbows and knees, involvement of the scalp, the lumbosacral region and the umbilicus

morphology: red or salmon pink papulosquamous plaques covered by white or silvery scales and surrounded by normal skin, an active disease is distinguished by the so-called "Koebner phenomenon" where pressure by a glass spatula causes the development of new lesions

special features: high prevalence of pruritus [524]

Guttate psoriasis

alias: eruptive psoriasis

occurrence: post-infectious, usually within 14 days after a *ß-haemolytic streptococcal* infection or a viral infection, affecting children and adolescents

distribution: on the trunk

morphology: sterile pustules of a yellow-brown color

special features: self-limiting within a couple of months, but with unknown long-term prognosis of developing classic plaque psoriasis

Palmoplantar pustulosis

alias: pustulosis palmaris et plantaris

occurrence: preferably affecting women (9:1) who are smokers (95%) and older than 40 years

distribution: on palms and soles

morphology: small papules

special features: co-occurrence with chronic plaque psoriasis (25%) and therefore rather a co-morbidity than a psoriasis subtype

Inverse psoriasis

alias: flexural psoriasis

distribution: on intertriginous sites

morphology: without scales

Psoriatic erythroderma

alias: erythrodermic psoriasis

distribution: on the entire cutaneous body surface

morphology: erythema and scaling

special features: can be life-threatening by hypothermia, hypoalbuminemia and cardiac failure; not only caused by psoriasis but also atopic dermatitis, drug eruptions and cutaneous T-cell lymphoma

Psoriatic arthritis

alias: arthritis psoriatica

occurrence: 25% of psoriasis patients [551], arthritis appears before skin lesions in 10% of the cases

distribution: distal interphalangeal joints, oligoarthritis, dactylitis and calcaneal enthesitis [175]

morphology: seronegative inflammatory arthritis

special features: the opinion that psoriatic arthritis is only a disease subtype with additional joint involvement is under challenge at the moment

Psoriatic arthritis has been in the focus of interest for several years now. As early as 1973, Moll and Wright established the first diagnostic criteria which are still widely used [312]. They include the main features of the disease like inflammatory arthritis, seronegativity and psoriasis. According to this, Moll and Wright defined five psoriatic arthritis types: polyarthritis, asymmetrical oligoarthritis, spondylitis, arthritis mutilans and distal interphalangeal predominant arthritis. In contrast to psoriasis per se, for psoriatic arthritis there have been even more attempts to create sensitive criteria. [312, 175]

The histological picture of psoriatic plaques is characterized by a thickened epidermis in combination with parakeratosis and elongated rete ridges. The equally characteristic inflammatory infiltrate is formed by dendritic cells, macrophages, T cells and neutrophil microabscesses. In addition, convoluted capillaries beneath the epithelium explain the erythema of psoriatic lesions. [331]

While the aspect of psoriatic lesions concedes the diagnosis, the extent of the disease can vary strongly. To assess the disease severity Fredriksson and Pattersson [140] invented the Psoriasis Area and Severity Index (PASI) in 1978. The said index is area-weighted for the main body areas consisting of head, trunk, upper extremities and lower extremities. It estimates erythema, induration and desquamation of the psoriatic lesions for each area and subsequently totals them to the final score.

According to van de Kerkhof 1997 [239], the condensation of various different aspects into one figure and an inaccurate assessment of body areas are weaknesses of the PASI. In addition, van de Kerkhof argues that quality of life scales should be established and combined with quantitative procedures to form an adequate measure of disease severity.

Instead of proposing a new measure, Louden et al 2004 [289] aimed to simplify the existing PASI by lowering the number of variables.

Apart from that, it remains unclear if disease severity correlates with the presence and intensity of pruritus. It is a fact, however, that pruritus is a frequent symptom in patients with psoriasis, especially psoriasis vulgaris [524]. Together with equally frequent embarrassment about the skin condition, side effects of drugs and other factors it impairs the quality of life of patients [331]. Still, it remains underestimated as other pruritic diseases like atopic eczema or uraemic pruritus show both a higher frequency and intensity of this symptom [524].

Concerning dependency on gender, both males and females are affected equally [46] except for palmoplantar pustulosis where females are preferably affected [158]. In terms of disease onset, psoriasis can basically occur at any age but usually sooner rather than later [158]. Nevitt and Hutchinson 1996 [332] observed a mean age at onset of 33 years in psoriasis vulgaris patients, three-quarters showing an onset before the age of 46 years.

Henseler and Christophers 1985 [179] found two onset peaks in 2147 German psoriasis patients, an earlier one at the age of 16 years (women) or 22 years (men) and a later one at the age of 60 years (women) or 57 years (men). Based on this finding they claimed the disease onset to be bimodal with an early-onset (type 1) at ages < 40 years and a late-onset (type 2) at ages > 40 years. The distribution of their cohort according to these onset types showed a higher percentage of early-onset cases for both males and females. [179]

Early-onset:	74.2% (males)	Late-onset:	25.8% (males)
	66.4% (females)		33.6% (females)

The said types do not only differ in age of onset, but also in other clinical and epidemiological features. For example, at least one parent was affected in 50% of early-onset patients while none was affected in late onset patients. In addition, early-onset disease shows a more irregular course and a stronger tendency to generalization. Consequently, there seem to be two different forms: one hereditary early-onset form and one sporadic late-onset form. [179]

Concerning the prevalence of psoriasis, Raychaudhuri and Farber 2001 [389] published a survey on epidemiological reports worldwide. They claimed that psoriasis is more common in northern countries which show colder climates than in tropical regions. Their hypothesis that the Caucasian race is more frequently affected than other races was supported by studies carried out in European countries, North America and Canada. They reported high prevalences for countries like Germany (6.5%), Ireland (5.5%) and Scotland (4.8%) along with a very high prevalence for Kazach'ye in the Arctic region (11.8%) [131].

In Kenya, a country in eastern Africa where the climate is dry and rainless, the prevalence of psoriasis was reported to be 3.5% while Nigeria, a country in western Africa where the climate is rather humid and rainy, psoriasis showed a prevalence of only 0.08-0.4% [104]. Similarly low was the prevalence in Chinese populations, varying between 0.2% and 1.5% in different regions [131].

In summary, the prevalence of psoriasis varied substantially between countries and ethnicities ranging from less than 1% to over 10%. This wide variation even within countries, proposes environmental factors for disease expression.

1.2.2. Pathogenesis and etiology of psoriasis

The pathogenesis of psoriasis is very complex involving a huge number of different cells, regulatory proteins, pathways and checkpoints. It is described as an interplay between the immune system and the skin epithelium, initiated by environmental and genetic factors. Nestle et al 2009 [331] gave a comprehensive overview of the disease mechanisms leading to the development of psoriasis by summarizing relevant research results. The main aspects of this article shall be cited in the following paragraphs.

As psoriatic lesions showed a high density of immune cells and mediators, drugs targeting the immune system showed a superior effectiveness and bone marrow transplantation were able cure or transfer the disease, the immune system has been in the focus of interest since the 1970s.

Especially a dysregulated innate immune system is under discussion. Hereby, dendritic cells and interferon-α represent key cells and key mediators. In addition, keratinocytes are deeply involved in many different ways as well. First, they produce antimicrobial peptides like LL-37 cathelicidin, β-defensins and S100A7 (psoriasin) which activate plasmacytoid dendritic cells. Second, they are stimulated by mediators produced by TIP dendritic cells (TNF-α, interleukin-23 and nitric oxide) and T cells (TNF-α, interferon-γ, interleukin-17A, interleukin-17F and interleukin-22). In response, they release proinflammatory cytokines like TNF-α, interleukin-1 and interleukin-6 and chemokines like CXCL8 through CXCL11 and CCL20 together with antimicrobial peptides.

During the inflammatory process of the disease a transition from the innate to the adaptive immune system takes place. Myeloid dermal dendritic cells are activated by innate immune cells (mainly mediated by interferon-α) and subsequently induce the differentiation of adaptive immune cells. Hereby, interleukin-12 leads to the production of Th1 cells and interleukin-23 to the production of Th17 cells. These helper T cells activate keratinocytes, mediated by TNF-α and interferon-γ in the case of Th1 cells or by interleukin-17A, interleukin-17F and interleukin-22 in the case of Th17 cells. The keratinocytes in turn produce antimicrobial peptides, proinflammatory cytokines and chemokines which feed back to the innate immune cells and thereby complete the proinflammatory disease circle.

Thus, besides keratinocytes and dendritic cells, T cells play a key role in the pathogenesis of psoriasis. Especially Th17 cells have recently moved into focus, because they produce interleukin-22 which leads to the proliferation of keratinocytes. By this, the adaptive immune system is linked to an epithelial dysregulation.

Cytokines like interleukin-22 are key mediators in psoriasis which run together in common checkpoints of chronic inflammatory diseases. For example, interferon-α and interferon-γ converge with interleukin-23, interleukin-12 and interleukin-22 in the JAK-STAT pathway. Another proinflammatory cytokine, TNF-α, uses the NF-κB pathway instead.

In terms of counterregulatory mechanisms against these proinflammatory states, there is still research to be done. According to current studies, regulatory T-cells and interleukin-10 seem to be of importance though.

In addition, vascular endothelial growth factor (VEGF) and angiopoietins produced by endothelial cells seem to play a role in the pathogenesis of psoriasis. An excessive angiogenesis promotes the formation of a leaky microvasculature which in turn lets leukocytes migrate easily into inflamed skin. This in turn, pushes the course of inflammation.

In summary, Nestle et al 2009 [331] divide the pathogenesis of psoriasis into three stages: triggering of the disease by predisposing factors, initiation of the disease by a cascade including keratinocytes, dendritic cells and T cells and maintenance of the disease by processes involving various cell types and mediators.

During the first stage, the disease is triggered by environmental and genetic factors. Hereby, environmental factors involve physical trauma, stress, microorganisms (especially bacteria and their products), drugs and smoking while genetic factors involve predisposing genotypes like for example in the PSORS1 locus on chromosome 6. The coincidence and interaction between these factors can lead to stressed keratinocytes and thus trigger the disease initiation.

In the second stage, the stressed keratinocytes start a cascade by activating plasmacytoid dendritic cells which in turn activate dermal myeloid dendritic cells by the secretion of interferon-α. This leads to the differentiation of helper T cells (Th1 and Th17) and cytotoxic T cells (Tc1 and Tc17) in lymph nodes which recirculate and migrate into the skin.

During the third and last stage, various different processes lead to disease maintenance. For example, helper T cells Th1 and Th17 are presented with putative autoantigens causing them to stimulate dermal myeloid dendritic cells and keratinocytes in turn. TIP dendritic cells secrete proinflammatory mediators like TNF-α, interleukin-23 and nitric oxide leading to keratinocyte activation and proliferation. In addition, natural killer T cells and neutrophils are attracted by chemokines while macrophages help dendritic cells and T cells to build perivascular clusters.

At the same time, fibroblasts secrete a multitude of growth factors including epidermal growth factor (EGF), keratinocyte growth factor types 1 and 2 (KGF-1/2) and transforming growth factor β (TGF-β) which lead to epidermal proliferation. The vascular endothelial growth factor (VEGF), on the contrary, promotes T cell migration and by this contributes to the maintenance of the disease.

Since this comprehensive review by Nestle et al 2009 [331], further insights into the pathogenesis of psoriasis have been gained. A review by Coimbra et al 2012 [99], for examples, found that the interleukin-23/Th17 axis is not only involved into the disease mechanism but crucial for the development of the disease. In addition, Cai et al 2012 [59] presented further T cell populations which might play a role in the pathogenesis of psoriasis. They discussed regulatory T cells as well as newly identified dermal $\gamma\delta$ T cells which produce interleukin 17.

Wolf et al 2012 [531], in contrast, focused on possible causes for the epidermal barrier dysfunction. They found that both an inhibition of epidermal transglutaminase and a disturbance of lipid/cholesterol/ceramide synthesis are possible candidates for epider-

mal hyperproliferation or hyperplasia with subsequent barrier dysfunction. A faulty defence or an incorrect reaction to penetrating microorganisms, however, did not seem to contribute to the pathogenesis.

As the disease is triggered by environmental and genetic factors, its etiology is referred to as multifactorial or complex. While the involvement of environmental factors was substantiated by a regionally varying prevalence within countries, twin studies provided initial proof of underlying genetic factors by showing higher concordance rates in monozygotic than in dizygotic twin pairs [539, 116]. Since then, the genetic component of psoriasis has been intensely researched accumulating a large amount of data. An analysis of this data on genetic predispositions to psoriasis forms the second part of this work.

1.3. Similarities - is a shared genetic background conceivable?

The most obvious common ground of atopic eczema and psoriasis is that both are chronic inflammatory skin diseases. When studying the diseases in detail, there are a number of similarities, but also differences to be considered. In the following, distinctive features concerning clinical and histological appearance, epidemiological data as well as pathogenesis and etiology shall be discussed and evaluated as to whether a shared genetic background is conceivable.

Relating to the clinical features of atopic eczema and psoriasis, there are several similarities and differences to be witnessed. First of all, the morphology of the diseases is not dissimilar, especially guttate psoriasis is a differential diagnosis of atopic eczema [355]. In addition, adult phase atopic eczema can show dry, scaly plaques similar to psoriatic plaques. Regarding the distribution of skin lesions, both diseases can affect the scalp and extensors. Yet atopic eczema shows extensor involvement only in infants and children while adults show lichenification in flexural folds. While psoriasis in general does rather show extensor involvement, inverse psoriasis poses an exception by affecting intertriginous sites.

The histological picture of psoriatic plaques and chronic eczematous patches is actually quite similar. It shows a thickened epidermis and an inflammatory infiltrate mainly consisting of dendritic cells, T cells and macrophages. In atopic eczema there are additional monocytes and eosinophiles to be found and in psoriasis neutrophil microabscesses. While parakeratosis and elongated rete ridges are further striking characteristics of psoriasis, acute eczematous lesions show a spongiosis due to epidermal intercellular edema.

Both diseases can manifest as mild to severe forms and affect the quality of life by symptoms like itching, embarrassment for the skin condition or complications. Pruritus is more pronounced in atopic eczema, but not to be underestimated in psoriasis as well [524]. Feared complications are secondary infections, yet patients with atopic eczema seem at greater risk. Especially cutaneous infections by *Staphylococcus aureus*, *herpes*

simplex and *molluscum contagiosum* are very common [448]. In contrast, psoriasis is rarely complicated by bacterial, viral or fugal superinfections [23].

The onset of symptoms is usually earlier in atopic eczema where the disease manifests during the first six months of life [448]. Psoriasis, on the contrary, shows two peaks of disease onset. The first between 16-22 years and the second between 57-60 years, forming an early-onset and a late-onset type [179]. Both psoriasis and atopic eczema show a chronic or chronic relapsing course of disease, the latter changing its distribution and morphology during three sequential phases from infancy to adulthood [448].

The prevalence of both chronic inflammatory skin diseases is similarly high, especially in northern European countries while lower frequencies are witnessed in China. The prevalences show a great variation from less than 1% to over 10% (psoriasis) or even 17% (atopic eczema). Concerning dependency on gender, a slight shift in the female/male ratio was found for atopic eczema (1.3 : 1.0) while men and women were equally affected with psoriasis.

Concerning the mechanisms leading to the clinical pictures of atopic eczema and psoriasis, a number of similarities but also some important differences have to be considered. A dysfunction of the epidermal barrier as well as a dysregulated T cell response are indispensable for the pathogenesis of both diseases. As a consequence, cells like keratinocytes, dendritic cells and regulatory T cells are involved in any case. Concerning enzymes, proinflammatory cytokines including TNF-α, interleukin-1 and interleukin-6 play an important role in both atopic eczema and psoriasis.

Some differences can be witnessed in the T cell response. In psoriasis, naive helper T cells mainly differentiate to Th1 and Th17 cells producing interferon-γ and interleukin-17A, interleukin-17F and interleukin-22, respectively. In atopic eczema, a Th2 cell and related interleukin-4 predominance can be seen in acute lesions while mainly Th1 cells like in psoriatic skin are present during the chronic phase of the disease. In addition, the latest findings suggest an involvement of Th17 and Th22 cells in atopic eczema. The number of Th17 cells seems to be lower in atopic than in psoriatic lesions, however.

Relating to etiology, both diseases show a multifactorial genesis being triggered by environmental and hereditary factors. The latter show striking parallels as the development of lesions is influenced by mechanical irritation like scratching in atopic eczema and by physical trauma like pressure (Koebner phenomenon) in psoriasis. Moreover, microorganisms and their products can affect the epidermal cells thereby promoting psoriatic lesions, while especially *Staphylococcus aureus* and its enterotoxins play an important role in the pathogenesis of atopic eczema.

Concerning the involvement of genetic factors, twin studies showed higher concordance rates in monozygotic than in dizygotic twins for both diseases. As a consequence, there was a lot of research in this area accumulating data on the genetic predispositions to atopic eczema and psoriasis. While the first two parts of this work analyse these data separately, the third part compares them to each other evaluating the presence of a shared genetic background.

The hypothesis of a shared genetic background was proposed as risk loci had shown an overlap in genome-wide linkage studies in the first place [100]. Yet atopic eczema and psoriasis show further similarities concerning appearance and pathogenesis which shall

be summarized at this point.

As mentioned, shared clinical features are dryness and scaliness of the skin combined with inflammation. Similarly, the histological pictures of both psoriatic lesions and chronic eczematous lesions show a thickening of the epidermis as well as an inflammatory infiltrate.

The pathogenesis of both diseases involves an epidermal dysfunction and a dysregulation of the T cell response. Hereby, Th1 cells are present in psoriasis and during the chronic phase of atopic eczema while keratinocytes, dendritic cells and regulatory T cells are entangled in the mechanisms of both diseases just like proinflammatory cytokines including TNF-α, interleukin-1 and interleukin-6. Taking into account these similarities, a shared genetic background of the two chronic inflammatory skin diseases seems conceivable.

2. Methods

The analysis of data on genetic predispositions to psoriasis and atopic eczema was carried out in different stages. First, the results of all association studies including genome-wide scans on either psoriasis or atopic eczema were summarized in large surveys in order to provide a complete picture on current genetic research. In the second stage, the attention was turned to genetic variants which had been analysed most frequently. If there were sufficient replications, meta-analyses comparing the results of association studies and combining them to an overall estimate were performed. Lastly, gained insights into the genetics of psoriasis and atopic eczema were compared to each other.

The general strategy of preparing the comprehensive surveys of genetic predispositions and arranging the specific meta-analyses of genetic variants was similar. First, a comprehensive search was performed in order to identify eligible studies. Next, relevant publications were selected by introducing inclusion criteria and stored into databases together with crucial information gained by data extraction. For the surveys, positive and negative reports were arranged into different tables in order to provide an overview. In the case of meta-analyses, a further statical estimation was conducted in order to quantify the results.

2.1. Survey of genetic predispositions

As mentioned above, the first stage aims to provide a comprehensive overview of the genetic predispositions to atopic eczema and psoriasis. There has been a lot of research in this area as both are known as multigene diseases. While genetic linkage studies tried to define susceptibility loci, association studies aim to assess the direct correlation between genetic polymorphisms and the disease. Genome-wide association studies (GWAS) are able to investigate many polymorphic sites at the same time using large case-control samples. These approaches accumulated a lot of data on genetic predispositions over the last years.

2.1.1. Identification of eligible studies for the survey

To provide a full picture of the genetic predisposition to atopic eczema on the one hand and psoriasis on the other hand, two independent searches were conducted on *MEDLINE*[1]. The last search update was carried out in January 2011. In order to get as many relevant studies on the genetic susceptibility to atopic eczema and psoriasis as possible, various search terms were tested.

[1]National Library of Medicine, Bethesda, Maryland, since 1966

After the trial of different combinations, the following strings were found to produce the best results for the respective diseases:

- (atopic eczema OR atopic dermatitis) AND (polymorphism* OR snp*)
- psoriasis AND (polymorphism* OR snp*)

These rather global search terms were used on purpose, as the data on genetic predispositions should be as complete as possible. Hence, the 307 results for atopic eczema and the 488 results for psoriasis included some irrelevant data as well. Despite the key words *atopic eczema/atopic dermatitis* and *psoriasis*, several studies on different diseases had to be excluded together with articles on gene expression, drug design or animal models. Review articles helped to identify additional genetic associations referencing studies with original data. Sometimes the accessibility of articles presented a problem, if they were published in foreign-language journals or in journals that were not available in the following libraries: Technical University Munich, Ludwigs-Maximilians-University Munich or Bavarian State Library.

Nevertheless, the ambitious goal was to include as much relevant data as possible. Consequently, both positive and negative reports were included whereas the identification of the former was much easier. If evidence of an association between a polymorphism and a disease was gained, the authors stated it directly in the corresponding title or abstract. If no evidence was gained, however, the information had to be searched throughout the article. In some cases, negative results were only provided in tables or they were not provided at all. Thus, publication bias has to be considered as a potential confounder.

2.1.2. Inclusion criteria for the survey

In order to comply with some of the difficulties mentioned above, a couple of inclusion criteria were defined. They serve to exclude irrelevant results on the one hand and to standardise/restrict relevant results on the other hand. As a consequence, all studies admitted to the survey had to comply with the following requirements:

- Studies had to be published in an accessible English-language journal.
- Studies had to provide original data, review articles were excluded from the survey.
- Studies had to investigate associations in atopic eczema/psoriasis.
- Studies had to show a case-control design using unrelated cases and controls or a family design using sets of parents and offspring.
- Studies had to provide the sample size.
- Studies had to state whether an association between the polymorphism and the disease had been detected or not.

- Studies had to investigate single nucleotide polymorphisms (SNPs) or copy number variations (CNVs), approaches using microsatellite markers were excluded from the survey (apart from a few exceptions).
- Studies had to investigate independent polymorphisms, haplotype analyses were excluded from the survey (apart from a few exceptions).
- Polymorphisms had to be named in any way, best via base number (*GenBank*[2]) or SNP ID (*NCBI SNP database*[3]).

2.1.3. Data extraction for the survey

The execution of the said inclusion criteria led to a smaller but still large data volume which had to be stored in an appropriate and clear-arranged form. For this purpose, data was split into positive and negative reports which were defined as follows:

Positive reports: Studies which investigate polymorphisms providing evidence of association in at least one published study

Negative reports: Studies which investigate polymorphisms lacking evidence of association in every published study

These two kinds of reports were stored in separate databases providing different extents of information. More information was obtained from studies which investigated polymorphisms with evidence of association (positive reports): First, the genetic variant in question was characterized by its name and exact location in the genome. In addition, the gene symbol was provided if the polymorphism belonged to a gene. Second, the study itself was characterized by the country where the participants reside, the sample size (number of cases in case-control studies or number of families in family studies) and the outcome. Studies on atopic eczema were further categorized regarding age of participants and/or disease characteristics while studies on psoriasis were further categorized regarding clinical psoriasis variant and/or onset type.

In contrast, data extraction from studies on polymorphisms lacking evidence of association (negative reports) was less extensive. Only the name and location of the genetic variant and the name of its corresponding gene were extracted.

2.2. Meta-analyses of well-studied genetic variants

During the preparation of the surveys for atopic eczema and psoriasis, it became clear that some genetic variants had been analysed much more frequently than others. For

[2]genetic sequence database produced and maintained by the National Center for Biotechnology Information (NCBI) as part of the International Nucleotide Sequence Database Collaboration (INSDC)

[3]archive for genetic variation developed and hosted by the National Center for Biotechnology Information (NCBI) in collaboration with the National Human Genome Research Institute (NHGRI)

these well-studied genetic variants, the performance of meta-analyses appeared to make sense. Hence, the surveys were searched for large sets of studies dealing with the same polymorphism. After their identification, the sets of studies had to fulfill certain inclusion criteria before relevant data could be extracted and meta-analyses could be performed.

2.2.1. Identification of eligible studies for the meta-analyses

As mentioned, the survey of all investigated polymorphisms was scanned in order to identify sets of studies investigating the same polymorphism. Moreover, all references mentioned in these studies were reviewed for additional studies not indexed in *PubMed*. For the inclusion in a meta-analysis, each study had to comply with some further requirements mentioned below and a minimum of six studies had to be included in a meta-analysis to achieve sensible results.

2.2.2. Inclusion criteria for the meta-analyses

As most studies were extracted form the surveys, the inclusion criteria mentioned in subsection 2.1.2 are still relevant. In order to produce consistent meta-analyses, however, restrictions were made regarding study design as the two kinds of association studies, family analyses and case-control analyses, are generally difficult to compare. For this reason, only one of them was included in the meta-analyses and the decision fell on case-control studies as they were more frequent.

In addition to that, precise and quantifiable data is needed to perform meta-analyses. For the surveys it had been sufficient to state if there had been an association or not. For the meta-analyses, however, only concrete numbers representing the inter-relation between genetic variants and disease allow a quantitative comparison and the calculation of an overall estimate. Consequently, the inclusion criteria in subsection 2.1.2 had to be extended by the following points:

- Studies had to be of a proper case-control design.
- Studies had to show a sample size of at least 100 subjects.
- Studies had to provide sufficient data
  - to calculate odds ratios, confidence intervals and p values using
    - allele frequencies,
    - genotype frequencies,
    - allele distribution or
    - genotype distribution in a complete contingency table;
  - or to extract odds ratios, confidence intervals and p values.
- Studies had to show a risk allele frequency of at least 1%.

2.2.3. Data extraction for the meta-analyses

Genotyping data and further characteristics of the study sample had to be extracted from each publication. The said characteristics are important for the comparison of different association studies as they might give hints for specific relations or interfering factors. Some basic information had already been extracted for the surveys, including the first author, year of publication, country where the patients reside and number of patients (see subsection 2.1.3).

For the calculation of pooled estimates, further information like number of controls and risk allele frequency in patients and controls was needed. If this information was not provided in the study, the frequency was estimated from allele or genotype distributions.

As mentioned, further characteristics such as ethnicity, mean age at participation and percentage of male patients were obtained wherever available in order to detect specific associations or confounding factors. In the case of psoriasis, most studies provided additional information like mean age at onset, percentage of early-onset psoriasis and specification of the clinical psoriasis variant. To provide an overview, the said data was extracted from the studies and arranged in tables.

2.2.4. Statistical analysis of the meta-analyses

The data extraction was followed by a statistical analysis in order to quantify the effect of genetic associations. The individual results of all studies dealing with the same genetic variant were used to calculate an overall estimate. For this purpose, the outcomes of the different studies had to be matched. This was achieved by defining a risk allele and a genotype model creating a specific setting to recalculate the individual association estimates. This calculation was put into practice by *StatXact 8* software based on 2x2 contingency tables, generating odds ratios (ORs) as association estimates together with confidence intervals (CIs) and p values. In most of the cases a multiplicative genotype model was used. As a consequence, the contingency table had to provide the following information:

- number of cases carrying the wild-type allele (A = 2AA + AB)
- number of cases carrying the mutant allele (B = 2BB + AB)
- number of controls carrying the wild-type allele (A = 2AA + AB)
- number of controls carrying the mutant allele (B = 2BB + AB)

If contingency tables were available in the individual studies, they were reshaped according to the desired genotype model. In case of a missing contingency table, it was created by using allele or genotype frequencies and numbers of patients and controls. In *StatXact 8*, the binomials were considered as being independent for the estimation of exact odds ratios and confidence intervals while *Fisher's exact test* was applied to calculate two-sided p values. In case no raw data was provided, association estimates

matching the chosen risk allele and genotype model were directly adopted from the study.

In the next step, meta-analyses were performed using *StatsDirect* software. By default pooled estimates were calculated for both a random effects model (*DerSimonian-Laird*) and a fixed effects model (*inverse variance*). To choose the appropriate model the non-combinability of studies was evaluated. If *Cochran's Q test* showed a significant ($P < 0.05$) inconsistency of studies, a random effects model was applied. If the result of *Cochran's Q test* was insignificant ($P \geq 0.05$), however, a fixed effects model was applied.

The output of *StatsDirect* involves a forest plot showing the individual estimates together with the pooled estimate of the meta-analysis. Hereby, the distribution of individual estimates may be indicative of inconsistency, confounding factors or specific associations. Another part of the output is a funnel plot which indicates publication bias by an asymmetrical shape. If *Egger's regression test* shows a significant deviation from the symmetry assumption ($P < 0.05$), bias due to predominant publication of positive results must be assumed.

Wherever appropriate, additional meta-analyses on coherent subgroups of study samples were carried out, especially according to ethnicity, clinical variant or onset type. These separate analyses were able to detect or validate specific associations depending on one of the said characteristics. They were performed if subgroups involved a minimum number of four study samples. As a consequence, small sizes of subgroups and missing information on characteristics limited the number of such refined analyses.

2.3. Comparison of genetic predispositions

After analysing the genetics of atopic eczema and psoriasis separately, they were compared to each other. This comparison was carried out in different stages, moving from general to specific. First, results of genetic linkage analyses were considered. The locations of established susceptibility loci and additional linkage regions were outlined in a karyogram and subsequently investigated with regard to overlaps.

Next, results of genetic association studies were examined. In oder to identify matches, the surveys of genetic predispositions were scanned for significant associations in overlapping chromosomal locations. These findings were collected into a comprehensive table and visualized by karyograms. After discussing shared chromosomal locations with divergent candidate genes, shared candidate genes were considered more closely. They were tabulated together with respective genetic variants and the according number of significant associations.

In addition to these shared positive reports on genetic predispositions, common negative reports were considered as well. By this, candidate genes which seemed highly relevant for the pathogenesis of chronic skin inflammation but lacked association could be identified. Furthermore, contrasting reports on genetic predispositions were of interest. The coincidence of positive reports for one disease with negative reports for the other disease might indicate independent risk factors.

3. Genetic predispositions to atopic eczema

Today it is common knowledge that atopic eczema is a complex disease with a multifactorial genesis. Both environmental and hereditary factors contribute to the development of the disease. Especially a regionally varying prevalence within countries and an increasing incidence over the past decades imply environmental factors for disease expression. For example, the development of eczematous lesions is influenced by mechanical irritation like scratching or by colonization with *Staphylococcus aureus*.

The first evidence of genetic factors underlying the development of atopic eczema was provided by twin studies. Larsen et al 1986 [266] and Schultz Larsen 1993 [423] involved 592 and 812 twin pairs from Denmark, respectively. Their reported concordance rates were higher for monozygotic twins (72%/86%) than for dizygotic twins (21%/23%), the former being more often concordant than the latter. A few years later, elevated IgE levels showed a high degree of heredity (approx. 50%) indicating a critical role for genetic factors [365].

Dold et al 1992 [111] analysed 6665 German families in order to asses the risk of developing atopic eczema for children with atopic family history. Their results showed that parental atopic eczema was the greatest risk factor (OR = 3.4). Parents with other atopic diseases including allergic rhinitis and asthma conferred a lower risk (OR = 1.4 and OR = 1.5, respectively). This implies the presence of specific genetic risk factors for atopic eczema.

Quite a few genetic predispositions to atopic eczema have been identified over the past decades. The corresponding levels of evidence vary, however, reaching from single positive reports through replicated reports up to multi-stage genome-wide association studies and robust meta-analyses. As a consequence, a comprehensive survey shall summarize all reports and their replications in order to give an overview on the current status of genetic research. In addition, meta-analyses on well-studied genetic variants shall be performed in order to validate individual reports.

3.1. Survey of genetic predispositions to atopic eczema

The genetic research on atopic eczema passed through different stages using a number of different approaches. While twin studies promoted both heritable and environmental factors for the development of the diseases, genetic linkage analyses in families with atopic eczema proposed a couple of susceptibility loci. Since the discovery of the first locus in 2000, eight more loci have been identified over the past decade. Most of the

times, however, said susceptibility loci contain hundreds of polymorphic genes which could play a role in the pathogenesis of atopic eczema. This is why they are usually analysed in detail by fine-mapping in a second step. This in turn, can induce the discovery of so-called candidate genes.

Another approach uses knowledge on pathogenic pathways to identify candidate genes. The hypothesis that gene products contribute to the pathogenesis of atopic eczema is the idea of so-called candidate gene studies or association studies. Consequently, genes in connection with certain processes like inflammation, immune response or skin barrier function are in the focus of interest. Apart from their selection due to functional relevance, candidate genes can also be derived from related diseases like for example asthma.

In contrast to candidate gene studies which concentrate on specific genes and sites, genome-wide association studies (GWAS) are a more comprehensive way to identify genetic associations in the whole genome. As no previous knowledge on putative candidate genes is used, this approach is called "hypothesis-free". It has only been available for a few years now, but has already provided new insights.

In summary, all the discussed approaches lead to the identification of genetic predispositions to atopic eczema accumulating a large amount of data. In order to provide a comprehensive overview, the findings have been tabulated in a two-part survey. The first table involves all publications on genetic variants which have been associated with atopic eczema in at least one published study (Positive reports: Table A.1, p. 225) while the second table summarizes all genetic variants which have not shown evidence of association (Negative reports: Table A.2, p. 230). Genes with both positive and negative reports for different variants are marked with an asterisk.

In order to reproduce the creation of the survey, the strategies and findings of the different approaches will be discussed in more detail and striking results will be highlighted. First, susceptibility loci identified by genetic linkage analyses will be presented together with genetic predispositions mapping to them. Second, results of candidate gene studies will be described in exemplary form together with some background information. Third, genome-wide association scans and their findings will be discussed in order to complete the picture of genetic predispositions to atopic eczema.

3.1.1. Genetic linkage studies on atopic eczema

As mentioned, genetic linkage studies tried to establish risk loci for atopic eczema in the genome. And indeed, a total of nine susceptibility loci (ATOD1-9) have been discovered during the last twelve years. As most of these newly identified linkage regions contain a variety of polymorphic genes, fine-mapping was applied to locate promising candidate genes and variants.

In addition, it should be noted that the replication level of the said susceptibility loci varies widely. ATOD9, for example, has been replicated in three independent genome-wide linkage analyses while ATOD6 relies on the results of a single study. All loci except ATOD8 have been investigated in greater detail by fine-mapping or in candidate gene studies.

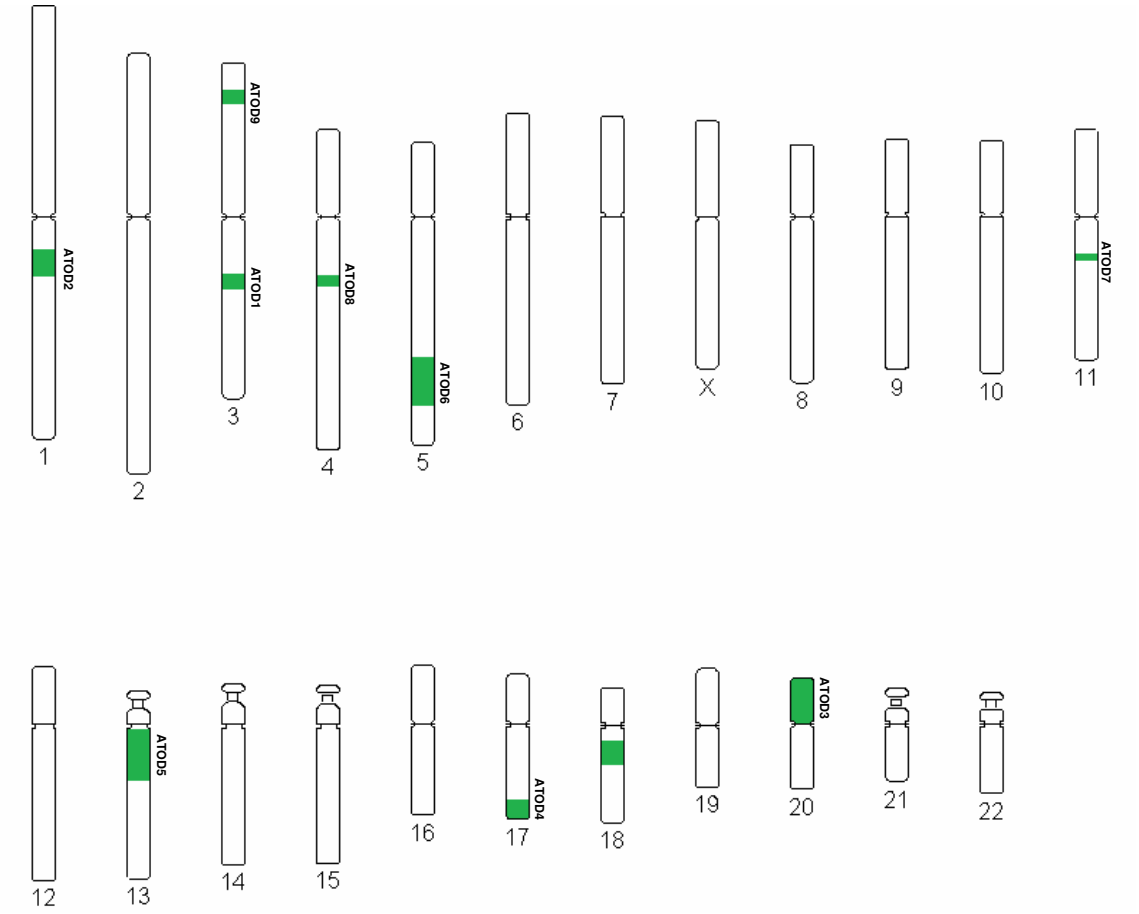


Figure 3.1.: Karyogram showing susceptibility loci for atopic eczema established by linkage analyses; ATOD1-9.

In the following, the discovery and replication of the said susceptibility loci by genetic linkage analyses as well as the identification of candidate genes in these regions shall be discussed. Besides, Figure 3.1 provides an overview on the chromosomal locations of the discussed atopic eczema risk loci.

ATOD1 (3q21)

A genome-wide linkage scan on European families by Lee et al 2000 [275] discovered linkage near microsatellite marker D3S3606 on chromosome 3q21. While a subsequent analysis by Cookson et al 2001 [100] was not able to confirm this finding, Christensen et al 2009 [96] detected a significant association between marker D3S3569 and chromosome 3q21.2. In spite of the replicated evidence of linkage, the region lacked reasonable candidate genes in the first place.

Later, a case-control study tested CSTA on 3q21 for association with atopic eczema and observed a significant result for the +344 C allele. The said gene encodes cystatin

A, an inhibitor of *Der p 1* and *Der f 1* from house dust mite. An impairment of this defense mechanism might favor sensitization and lead to allergic phenotypes including atopic eczema [494]. In spite of this, there was no attempt to replicate this potential candidate gene since then.

Shortly afterwards, Soderhall et al 2007 [442] performed a fine-mapping analysis trying to identify the disease-causing gene of ATOD1. Genetic markers led to a subregion containing a single candidate gene named COL6A5 (formerly COL29A1). It encodes a new collagen which contributes to protein-ligand interactions in the epidermis. Significant associations with genetic variants in COL6A5 were observed in two independent German family samples. Replication in another German case-control sample failed, however [167].

ATOD2 (1q21)

Chromosome 1q21 was proposed as atopic eczema susceptibility locus by Cookson et al 2001 [100]. It contains the epidermal differentiation complex (EDC) involving candidate genes like FLG, IVL, LOR, HRNR, the S100 family, the LCE cluster and SPRR genes (see section 3.1.2).

Among them, FLG is the most promising risk gene for atopic eczema. The results of several association studies have already been summarized and validated in two comprehensive meta-analyses (see subsection 3.2.3).

In addition, a genome-wide association scan by Esparza-Gordillo et al 2009 [129] supported filaggrin as the major candidate gene. Yet it provided evidence of additional risk factors in the EDC as well, as one marker near HRNR remained significant after stratification for FLG null mutations (see subsection 3.1.3).

ATOD3 (20p)

Cookson et al 2001 [100] found another significant linkage signal on chromosome 20p. Although the susceptibility locus was not replicated by other genome-wide linkage scans, a putative candidate gene was ascertained. ADAM33 on chromosome 20p13 was proposed due to its established association with other atopic disorders (see section 3.1.2). Matsusue et al 2009 [306] proved the hypothesis in 140 Japanese children with atopic eczema and 258 controls, but there was no replication so far.

As prodynorphin polypeptide is a precursor protein for pruritus-modulation opioid peptides, it was hypothesized as a candidate gene for atopic eczema as well. PDYN promoter polymorphisms on 20pter-p12, however, did not show association to Austrian atopic eczema patients and pruritus severity [157].

ATOD4 (17q25)

In addition to ATOD2 and ATOD3, Cookson et al 2001 [100] established a third atopic eczema susceptibility locus on chromosome 17q25. It was not replicated by another linkage study, but Bradley et al 2002 [49] gained evidence of linkage nearby on chromosome 17q21.

Concerning the identification of candidate genes in this region, Ekelund et al 2006 [119] proposed SOCS3. This gene encodes a suppressor of cytokine signaling and consequently might play a role in the pathogenesis. At first, a systemic analysis of global gene-expression patterns had shown an over-expression of SOCS3 mRNA in atopic eczema. Subsequently, genetic associations were established for rs12952093 and rs4969170 in Swedish family and case-control samples. A replication sample from the United Kingdom did not reach significance [119].

A RUNX-binding-site, between SLC9A3R1 and NAT9 on chromosome 17q25, did not show evidence of association with atopic eczema. The rs734232 polymorphism was equally frequent in Japanese patients and controls [196].

ATOD5 (13q12-14)

This susceptibility locus was initially described by Beyer et al 2000 [35] and later replicated by Bradley et al 2002 [49] (at least for 13q14). It contains a candidate gene named PHF11 which had previously shown association with elevated IgE levels and severe asthma (see section 3.1.2). For atopic eczema, a preferential transmission of two risk alleles was observed in an Australian family sample [217].

ATOD6 (5q31-33)

Beyer et al 2000 [35] described another susceptibility locus which was not replicated by linkage analyses but by candidate gene studies. Thirteen polymorphic genes on chromosome 5q31-33 were tested and nine showed significant associations. Especially IL13 provided a high number of positive reports for rs20541 (4257G/A) and rs1800925 (-1112C/T). The former variant was replicated in three independent cohorts and the latter in two (Table A.1, p. 225).

Two further candidate genes in this linkage region were derived from related diseases (see section 3.1.2). CD14, an established asthma risk gene, was associated with atopic eczema in three independent cohorts (Table A.1, p. 225). Yet there was not sufficient high-quality case-control data to perform a meta-analysis. For SPINK5, the gene underlying Netherton syndrome, the number of studies for atopic eczema was sufficient to perform a meta-analysis (see subsection 3.2.1).

A genome-wide association scan by Weidinger et al 2008 [519] evaluated the association of multiple markers with elevated serum IgE levels. RAD50 variants on 5q31 were consistently associated, but did not show a specific association with atopic eczema (see subsection 3.1.3).

In addition to the discussed candidate genes, there were further positive reports for interleukin genes like IL12B, IL5 and IL4 as well as for candidate genesADRB2 and CSF2 (Table A.1, p. 225).

ATOD7 (11q13.5)

This relatively new locus was not established by linkage analyses, but a genome-wide association scan. Esparza-Gordillo et al 2009 [129] had tested hundreds of marker SNPs

and one had gained genome-wide-significance on chromosome 11q13.5. The said polymorphism, rs7927894, maps to a candidate gene named C11orf30 (see subsection 3.1.3).

Further association studies focused on candidate genes with functional relevance. For example, GSTP1 on chromosome 11q13 encodes a glutathione S-transferase which might play an important role in the epithelial barrier function (see section 3.1.2).

MS4A2 (alias FCER1B) encodes the beta subunit of the high affnity immunoglobulin E receptor which triggers the inflammatory response in IgE-mediated diseases like atopic eczema or asthma [105]. Cox et al 1998 [105] found an over-transmission of RsaI-in2*2 and RsaI-ex7*1 in a panel of American families with atopic eczema and replicated this finding in a second panel. Yet two other studies did not support MS4A2 as a candidate gene [305, 185].

ATOD8 (4q22.1)

This linkage region was discovered by Christensen et al 2009 [96]. They had observed a significant association between the marker D4S2364 and atopic eczema severity. However, there is a lack of candidate genes in this susceptibility locus.

ATOD9 (3p24)

An overlap of linkage regions identified by Bradley et al 2002 [49], Haagerup et al 2004 [163] and Christensen et al 2009 [96] led to the establishment of ATOD9 on chromosome 3q24. But regarding candidate genes, there was merely a single positive report for IL5RA [327].

Additional linkage regions

Some of the genome-wide linkage analyses discovered further candidate regions outside of established susceptibility loci. For example, Bradley et al 2002 [49] reported association to 15q14-15 and 18q21. Linkage to the q arm of chromosome 18 was replicated by Haagerup et al 2004 [163] on 18q11-12 and Christensen et al 2009 [96] on 18q12, while further evidence of the q arm of chromosome 15 was gained by Enomoto et al 2007 [127] on 15q21. Moreover, Haagerup et al 2004 [163] added a locus on chromosome 4p15-14 and Guilloud-Bataille et al 2007 [162] two loci on 5q13 and 11p14.

3.1.2. Candidate gene studies on atopic eczema

In the following, genes and genetic variants identified by candidate gene studies with family or case-control design shall be discussed in exemplary form. These so-called candidate genes are characterized by at least two features: their location in the genome and their functional relevance. As seen in the previous section, many genes have been analysed because they were located in susceptibility loci for atopic eczema discovered in genome-wide linkage studies. Apart from that, candidate genes were selected due to functional aspects or an existing association in a related disorder.

Candidate genes for atopic eczema due to functional relevance

For choosing candidate genes the function of the gene product can give an important hint. As the pathogenesis of atopic eczema has become more and more uncovered during recent years, there is knowledge of disease pathways involving several proteins and other gene products. The involvement in such a pathway implies the contribution to the development of the disease. Hereby, genetic variants can lead to either impairing or protective effects.

For atopic eczema, there are two main components which contribute to the pathogenesis. It has long been known that a dysfunction of the epidermal differentiation, mostly a hyper-proliferation of keratinocytes, is crucial for the disease development. This promotes, for example, genes lying in the epidermal differentiation complex as putative candidate genes. Apart from skin hyper-proliferation, recent knowledge supports a dysregulation of the innate and adaptive immune response as another component of the pathogenesis. Thus, genes encoding immune mediators or other pro-inflammatory factors represent potential candidates for atopic eczema susceptibility as well.

Genes for epidermal differentiation. The epidermal differentiation complex (EDC) on chromosome 1q21 contains a number of genes which are, as the name implies, important for epidermal differentiation [449]. Mutations in these genes can consequently lead to a epidermal barrier dysfunction and by this contribute to the pathogenesis of atopic eczema.

The FLG gene was established as the number one risk gene in the EDC and for atopic eczema in general. Filaggrin supports the keratin cytoskeleton in epithelial cells and its breakdown products are needed for water-binding in the epithelium. Thus, a malfunction leads to a disturbed barrier function with increased transepidermal allergen penetration and water loss. Common FLG null mutations are one possible way how the efficiency of this protein can be impaired. [39]

As a consequence, various candidate gene studies have been performed on the said common FLG variants. In addition, the individual results have been validated in comprehensive meta-analyses and marker SNPs in linkage disequilibrium with FLG have shown association in a genome-wide association scan (see subsection 3.2.3).

Further candidates in the epidermal differentiation complex involve PGLYRP3, CRNN, IVL, LOR and HRNR as well as S100 genes, LCE genes and SPRR genes. All proteins encoded by these genes play a crucial role in epidermal differentiation and function like filaggrin. Hornerin, for example, is an S100 fused-type protein that forms part of cornified cell envelopes of the epidermis and consequently contributes to the barrier formation [178].

In spite of this functional relevance candidate gene studies were not able to confirm independent associations of any of these genes and atopic eczema (Table A.2, p. 230). A recent genome-wide association study, however, provided evidence of additional risk factors in the EDC apart from FLG null mutations. One significant marker was in LD with several genes involved in skin barrier function including cornulin (CRNN), late cornified envelope protein 5A (LCE5A) and especially hornerin (HRNR) (see subsection 3.1.3).

Genes encoding glutathione S-transferases. The so-called glutathione S-transferases are a family of enzymes which contribute to the detoxification of xenobiotic substances [413]. Thus, they might play an important role in the epithelial barrier function especially the resistance to pathogenic factors [502]. Safronova et al [413] was the first to study the relation between a gene encoding a glutathione S-transferase and atopic eczema. The association analysis yielded a significant p value for the GSTP1 variant Ile105Val in 117 Russian children with atopic eczema, 96 non-atopic controls and 61 randomized controls.

Shorty afterwards, the study group replicated their finding on GSTP1 in a further Russian sample set involving 126 children suffering from atopic eczema, 99 non-atopic controls and 100 randomized controls [502]. In addition to that, they investigated null mutations in GSTM1 and GSTT1 achieving similarly significant results.

The GSTP1 Ile105Val polymorphism was subsequently replicated in both a Korean [97] and a Taiwanese cohort [509]. The GSTM1 null allele showed successful replication in the Taiwanese cohort as well. While replication failed in the Korean cohort of Chung et al 2009 [97], it succeeded in another population from Korea involving both children and adults [92]. In contrast, all attempts to reproduce the finding on GSTT1 null mutation remained unsuccessful (Table A.1, p. 225).

Antimicrobial human β-defensin genes. As chemotactic effects on immature dendritic cells are attributed to the β-defensins, they might play a critical role in the pathogenesis of atopic eczema. They possibly link innate and adaptive immune system by attracting dendritic cells which determine the type of T cell response. [376]

In addition, an expression-analysis showed that human β-defensins, especially hBD-2, were over-expressed in lesional atopic skin [168]. Therefore, mutations in DEFB genes could be of functional relevance.

Prado-Montez et al 2007 [376] genotyped a Mexican case-control set for polymorphisms in DEFB1. Three SNPs involving 668C/G, 692A/G and 1654G/A showed evidence of association in 59 patients with atopic eczema and 151 matched controls. Two years later, Kim et al 2009 [240] tested a Korean cohort for DEFB1 variants. They found that two different SNPs (-2266T/C, -1241T/G) and the combined genotype were associated in 1098 case-control samples.

In contrast, Segat et al 2010 [424] reported that DEFB1 polymorphisms were not associated with atopic eczema in children and adolescent from northeast Brazil. They had genotyped 96 affected subjects and 191 healthy individuals for three different SNPs at 5'UTR of the said gene.

Mast cell chymase gene. Triggered skin mast cells produce a large quantity of a serine protease, the so-called mast cell chymase. This enzyme has a proinflammatory effect together with histamine and IgE, playing an important role in the pathogenesis of allergic and atopic skin inflammation. [301]

Mao et al 1996 [301] studied allelic polymorphisms in CMA1, the gene encoding mast cell chymase, assessing whether these could be organ-specific genetic risk factors for

atopy. And indeed, they found a significant association between the -1903 G (BstXI) polymorphism and atopic eczema in a Japanese cohort. After that, several replication studies were performed accumulating sufficient data to perform a comprehensive meta-analysis (see subsection 3.2.2).

Genes linked with cytokines. It is common knowledge that cytokines play an important role in the pathogenesis of atopic eczema. Interleukin-13, for example, promotes IgE secretion by B cells. If there is an imbalance towards Th2 cells which produce interleukin-13, this can lead to an allergic condition like in the pathogenesis of atopic eczema. [39]

A number of candidate gene studies have investigated mutations in the corresponding IL13 gene and their susceptibility to atopic eczema. There were positive reports for rs1800925 (-1112C/T) and rs20541 (4257G/A). The former was replicated two times and the latter three times, reaching a higher level of evidence (Table A.1, p. 225).

Interleukin-18 is another cytokine that plays an important role in the pathogenesis of atopic eczema. It promotes the switch from Th2 to Th1/Th0 predominance as it leads to the differentiation of Th1 cells together with interleukin-12. By this, they drive the transition from the acute phase to the chronic phase of atopic skin lesions. [39]

The question if genetic factors in the IL18 gene play a role in the susceptibility to atopic eczema, was investigated in several case-control samples. For the -137G/C variant there was successful replication in two individual cohorts from European descent while an association with Japanese individuals could not be confirmed (Table A.1, p. 225).

C-C chemokines are further potential candidate genes for the susceptibility to atopic eczema. They are believed to play an important role in the pathogenesis of allergic inflammation attracting and activating immune cells like eosinophiles. [333]

CCL5 (formerly RANTES) is one of the best investigated C-C chemokines in allergic diseases. Three independent case-control studies confirmed the association of -401G/A, a functional variant in the proximal promoter of CCL5, with atopic eczema. The cohorts included subjects from Germany [333] and Japan [466, 22] indicating similar susceptibility for European and Asian populations. A replication sample form Hungary did not reach statistical significance though [255].

As interferons contribute to the immune response in the skin and interferon regulator factor 2 (IRF-2) modulates cellular responses to interferons, mutations in the IRF-2 gene might be associated with atopic eczema susceptibility. [39]

Nishio et al 2001 [336] performed a family study in order to pursue this proposal. The IRF-2 variant -467G/A showed over-transmission in 49 family-trios from Japan. Yet this finding needs further confirmation in replication samples.

Thymic stromal lymphopoietin gene. The recruitment of T cells in the pathogenesis of atopic eczema is enhanced by the up-regulation of keratinocyte-derived thymic stromal lymphopoietin (TSLP) [39]. Consequently, Gao et al 2010 [146] hypothesized that genetic variants in TSLP could contribute to the susceptibility of the disease. They tested 27 SNPs in TSLP and in genes encoding its receptor. Variants rs10043985 and

rs2289276 were significantly associated in an African American cohort, while the frequency of variant rs11466749 differed significantly between cases and controls of an European American cohort. These findings have not been replicated yet.

Genes encoding toll-like receptors. Pattern recognition receptors like toll-like receptors (TLRs) recognize bacterial or fungal pathogens and initiate an innate immune response [1]. In addition, they can be stimulated by endogenous factors associated with allergic diseases [522] making a contribution of toll-like receptors to the pathogenesis of IgE-mediated disorders conceivable.

Investigations by candidate gene studies showed significant associations in one published study for TLR2, TLR4, TLR7, TLR8 and TLR9, respectively. Yet none of these positive reports was replicated to date (Table A.1, p. 225).

Candidate genes for atopic eczema derived from related diseases

Another way of selecting candidate genes is to look for reported associations in related diseases. As atopic eczema belongs to the circle of atopic disorders, both allergic rhinitis and asthma can lead to atopy-related genes. Still, most genes are organ-specific and do not necessarily show significant results for atopic skin lesions. In addition, a number of related skin diseases can give hints for genetic factors predisposing to atopic eczema as well.

Association of FLG with ichthyosis vulgaris. The two common FLG null mutations R501X and 2282del4 have been identified as causal factors for the monogenic skin disease ichthyosis vulgaris. Smith et al 2006 [435] investigated 15 families of European descent and found that the variants were semidominant with heterozygotes showing a milder phenotype than homozygotes and an incomplete penetrance. They also found that the loss-of-function mutations led to the disturbed keratinization observed in ichthyosis vulgaris.

Impaired keratinization being an equally common feature of atopic eczema suggested that FLG variants could be associated with this disease as well. This hypothesis was tested in a large number of candidate gene studies and two comprehensive meta-analyses, stating FLG as the number one risk gene of atopic eczema (see subsection 3.2.3).

Association of SPINK5 with Netherton syndrome. Another skin disease showing shared characteristics with atopic eczema is Netherton syndrome. It is a relatively rare trait with concomitant atopy and an autosomal recessive transmission. The disease causing gene was determined to be SPINK5, encoding the serine proteinase inhibitor LEKTI expressed in epidermal cells. [85]

Subsequent association studies for atopic eczema tested a number of coding SPINK5 variants. As most case-control studies investigated the amino acid exchange Glu420Lys, the number of studies was sufficient to perform a meta-analysis (see subsection 3.2.1).

Associations of CD14, PHF11 and ADAM33 with asthma. It is common knowledge that a common feature of atopic eczema and asthma is the dysregulated IgE response. As CD14 polymorphisms have shown to increase both asthma risk and IgE levels [25], a suspected association with atopic eczema has been evaluated in a number of candidate gene studies. The -159C/T variant was most frequently investigated, but there were not enough studies to perform a meta-analysis. Significant results were achieved for two cohorts from the United States and a German population. Yet two Dutch case-control samples, a German case-control sample and a family sample from the United States did not replicate this finding. One of the Dutch studies found an association with the variant -1619T/C instead. (Table A.1, p. 225)

Similar to CD14, Zhang et al 2003 [559] found replicated association of PHF11 variants with elevated IgE levels and severe asthma. PHF11 is expressed in immune cells and does probably play a role in chromatin remodelling or transcriptional regulation [217]. A significant over-transmission was witnessed in an Australian atopic eczema family sample for SNPs rs2247119 and rs1046295 [217]. Replication studies have not been published so far.

ADAM33, a membrane-anchored metalloprotease, was identified to be significantly associated with bronchial hyperresponsiveness and asthma in a genome-wide association study on 460 Caucasian families [492]. For atopic eczema, the rs2853209 variant showed increased susceptibility in a cohort of Japanese children [306]. Yet this was the only publication on the association of ADAM33 variants and atopic eczema.

3.1.3. Genome-wide association studies on atopic eczema

This hypothesis-free approach searches the entire genome for putative associations. It has been available for a few years now, but for atopic eczema the number of performed studies is still low. Interestingly, a genome-wide association scan by Weidinger et al 2008 [519] evaluated the association of multiple markers with serum IgE. Elevated levels are a common feature of atopic diseases, but not for atopic eczema in particular. They typed 353,569 SNPs in a discovery cohort of 1530 individuals and four additional replication sets from European origin.

Two FCER1A variants on chromosome 1q23 and multiple RAD50 variants on chromosome 5q31 were consistently associated with elevated IgE levels. However, they did not show a specific association with atopic eczema. As the number of atopic eczema cases was low, they tested another 562 family-trios from Germany. While no association with FCER1A variants was detected, there was evidence of a weak but significant effect in three RAD50 polymorphisms (P values = 0.007-0.01). This finding, however, was not replicated to date (Table A.1, p. 225).

The first genome-wide association scan on atopic eczema in particular was performed by Esparza-Gordillo et al 2009 [129]. They investigated European subjects in two discovery sets and two replication sets. In total, 3576 cases and 4932 controls as well as 270 nuclear families with two affected siblings were involved. The subsequent analysis comprised 342,303 markers which were distributed over the entire genome.

C11orf30 variant rs7927894. On chromosome 11q13.5 between C11orf30 and LLRC32, a single nucleotide polymorphism reached genome-wide significance in all sets combined (OR = 1.22, 95%CI = 1.15-1.30, P = 7.6E-10). As it forms a LD-block with C11orf30, the association is more likely derived from a genetic variant of this gene than of LLRC32. Interestingly, the rs7927894 A allele was associated with Crohn's disease as well [30].

One year later, O'Regan et al 2010 [356] replicated the finding using unrelated case-control data of 511 Irish children with atopic eczema and 1000 matched healthy controls (OR = 1.27, 95%CI = 1.09-1.49, P = 0.0025). Here again, the association was independent of FLG mutations showing a supplementary effect.

Nomura et al 2010 [344] evaluated the association of the rs7927894 A allele and atopic eczema in a non-European population. A number of 194 Japanese patients and 113 controls were genotyped for the polymorphism, but there was no significant difference in allele frequencies (0.129 vs. 0.115) suggesting no increased risk for Asian populations.

FLG and additional risk factors in the EDC. In the genome-wide scan of Esparza-Gordillo et al 2009 [129] another marker showed a genome-wide significant association for all cohorts combined. This marker, rs6661961, mapped to the epidermal differentiation complex (EDC) on 1q21 and was in high linkage disequilibrium (LD) with FLG null alleles at a distance of 156kb. The association lost significance when excluding FLG mutation carriers supporting FLG as atopic eczema risk gene.

Another marker located 78kb away from FLG, in contrast, remained significant after stratification for FLG variants. This association of rs877776 near HRNR indicates the presence of an additional risk factor in the epidermal differentiation complex apart from FLG. The marker was in linkage disequilibrium with hornerin (HRNR), cornulin (CRNN) and late cornified envelope protein 5A (LCE5A).

Discussion of the insights gained by genome-wide association studies. In summary, a number of additional genetic factors have been identified by this approach. On chromosome 5q31, there was evidence of association with RAD50 variants. Estimates were low, however, and there was no replication to date.

On chromosome 11q13.5, there was even more evidence of association for rs7927894 which is in linkage disequilibrium with C11orf30. It was consistently associated with atopic eczema in five independent sample sets form European descent. Replication in a Japanese cohort failed, suggesting different genetic factors in Asian populations.

On chromosome 1q21, there was both support for FLG as major atopic eczema risk gene and for additional genetic risk factors in the EDC. A single nucleotide polymorphism, rs877776, near the HRNR gene remained significant after stratification for common FLG null variants showing an independent association.

Figure 3.2 summarizes the replicated findings of genome-wide association studies (GWAS) on atopic eczema. It is important to keep in mind, however, that all these results were based on European populations only.

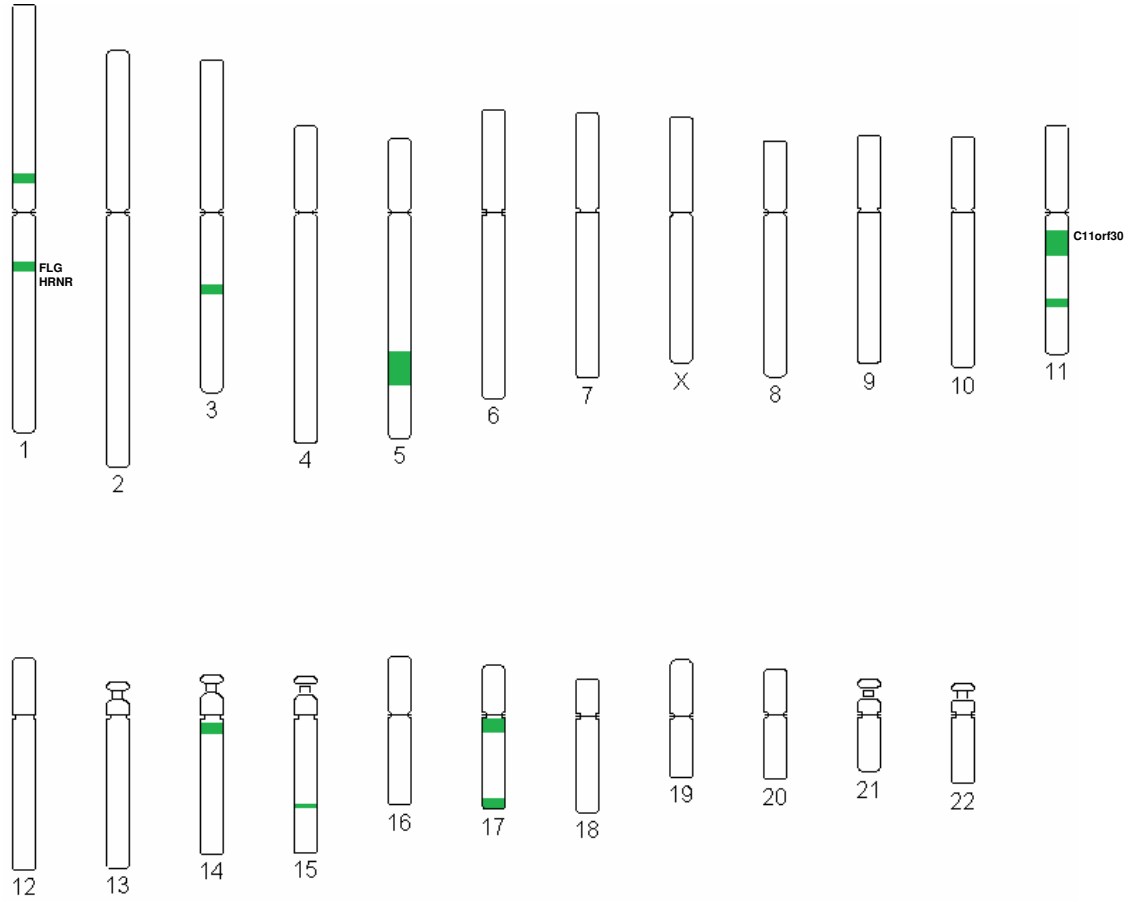


Figure 3.2.: Karyogram showing locations of genes with strict replications (in the same genetic variant) in high-quality studies for atopic eczema. Those replicated by genome-wide association scans are labeled.

3.2. Meta-analyses of well-studied genetic variants for atopic eczema

During the preparation of the survey, it became clear that some genetic variants had been analysed much more frequently than others. For these well-studied genetic variants, the performance of meta-analyses in order to validate the individual reports appeared to make sense. To achieve sensible results, a minimum number of six studies meeting the inclusion criteria was needed which was merely reached for three genes involving two single nucleotide polymorphisms and two null mutations.

Figure 3.3 shows the locations of these well-studied genes. While FLG maps to the epidermal differentiation complex on chromosome 1q21 and SPINK5 is located within the ATOD6 locus on chromosome 5q31-q33, CMA1 lies outside established risk loci.

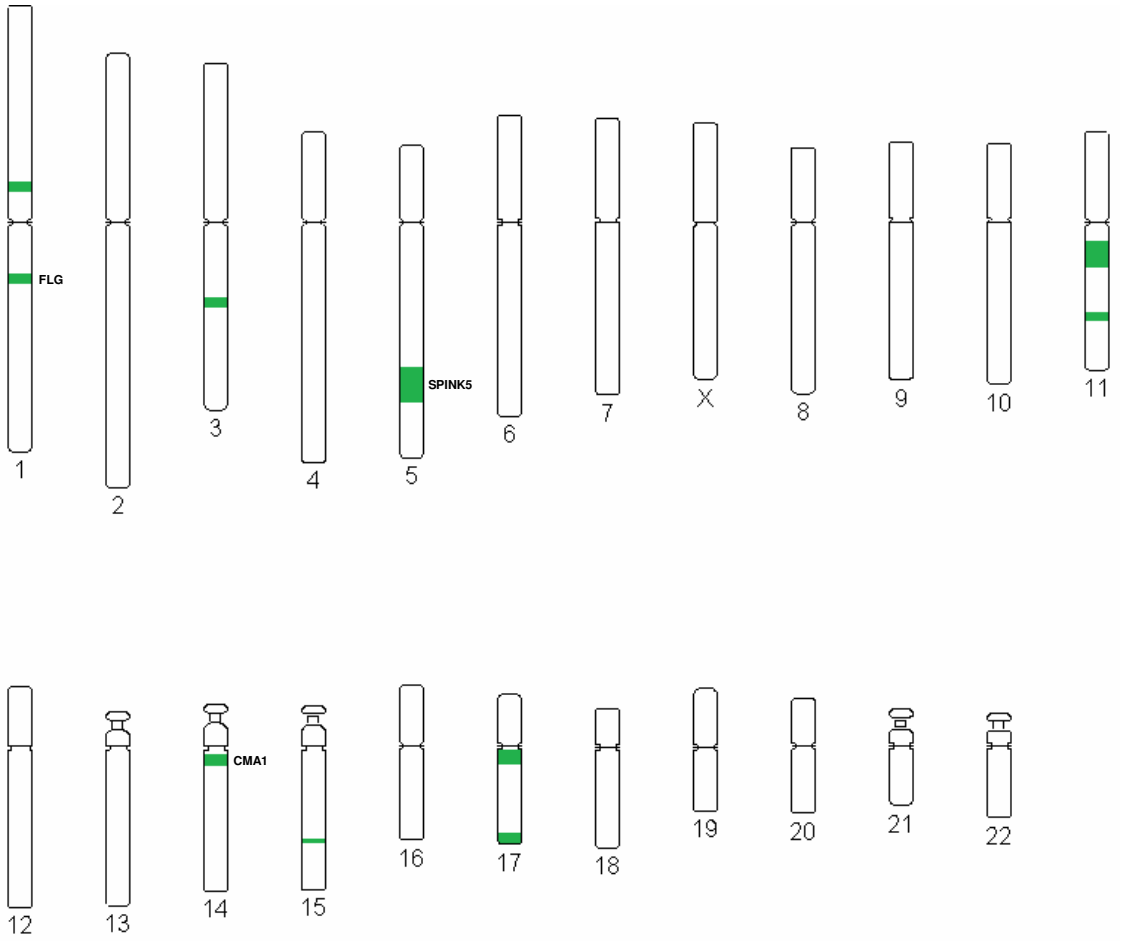


Figure 3.3.: Karyogram showing locations of genes with strict replications (in the same genetic variant) in high-quality studies for atopic eczema. Those investigated by meta-analysis are labeled.

In the following, all meta-analyses are listed according to their outcome. Investigations with negative results are followed by those with weak positive results and strong positive results. Newly performed meta-analyses are presented along with reports on existing meta-analyses.

3.2.1. SPINK5 variant rs2303067 (Glu420Lys)

As mentioned, this candidate gene was derived from a related disease. Initially, mutations in the SPINK5 gene on chromosome 5q32 were found to be associated with Netherton syndrome [85]. As this trait is an inflammatory skin disease showing concomitant atopy, an association with atopic eczema was suspected (see section 3.1.2).

Subsequent association studies for atopic eczema tested a number of coding SPINK5 variants. Yet most studies investigated the SNP rs2303067, also referred to as 1258G/A, which causes the amino acid exchange Glu420Lys. The number of case-control studies was sufficient to perform a meta-analysis.

Studies excluded from the meta-analysis. The first description of an association between SPINK5 1258G/A polymorphism and atopic eczema was based on the results of a family study by Walley et al 2001 [508]. They found a significant association of maternally derived alleles (Lys420) and atopic eczema in two family panels from the United Kingdom. Two years later another family study by Nishio et al 2003 [337] reported a preferential transmission of Lys420 alleles to offspring with atopic eczema in 41 Japanese families. These data from Asian and European populations indicate an association of the SPINK5 gene with atopic eczema across ethnicities.

Yet Folster-Holst et al 2005 [138] was not able to detect an association using 308 classical family trios from Germany another two years later. An additional case-control sample to replicate the finding was included in the meta-analysis. The study of Weidinger et al 2008 [518] described a weak effect for maternal transmission in 486 German families (OR = 1.25, 95%CI = 1.04-1.50, P = 0.01815). Here, too, a set of independent cases and controls were included in the meta-analysis.

A total of seven case-control studies were identified in the first place. However, three studies had to be excluded because of either missing genotyping information [224] or improper case-control design [261, 223].

Kabesch et al 2004 [224] analysed a German population and found a significant association of SPINK5 420Lys with 37 patients suffering from both atopic eczema and asthma (OR = 4.56, 95% CI = 1.37-15.12, P = 0.007). The significance disappeared, however, when considering patients with atopic eczema alone. Yet no genotyping data was provided to reproduce this finding.

Kusunoki et al 2005 [261] studied 118 Japanese children with mild to moderate or severe to most severe atopic eczema. A comparison of the genotype distribution indicated that both homozygotes (AA) and heterozygotes (AG) were more frequent in the severe to most severe atopic eczema group. These results account for an association of Glu420Lys polymorphism with disease severity. As there was no control population provided, however, this study could not be included in the meta-analysis.

Table 3.1.: Characteristics of studies included in meta-analysis of SPINK5 rs2303067 (Glu420Lys) variant in atopic eczema

		Numbers		Frequency		Mean Age (SD/range)		Male	
Author [Ref]	**Country**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**
Namkung 2010 [326]	Korea (A)	631	459	56.5	57.1	13.4 (9.9)	23.3 (2.2)	55.6	51.9
Weidinger-1 2008 [518]	Ger (E)	773	3992	-	-	-	49.5 (13.9)	40.1	49.9
Weidinger-2 2008 [518]	UK/Ire (E)	418	552	-	-	19.4 (18.4)	35.7 (12.3)	51.4	30.8
Weidinger-3 2008 [518]	UK (E)	1583	6063	-	-	3.5 (-)	3.5 (-)	53.6	51.7
Hubiche 2007 [198] $^{\Theta}$	France (E)	99	102	52.5	52.0	7 (0.2-68)	adults	65.7	100.0
Folster-Holst 2005 [138]	Ger (E)	201	368	66.0	64.0	-	-	-	-
Kato 2003 [233]	Japan (A)	124	110	61.0	55.0	28.7 (7-74)	35.0 (19-71)	-	-
Total		3829	11646	59.0	57.0				

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Frequency, frequency of the SPINK5 rs2303067 A allele in % ; Mean age, mean age of patients with standard deviation or range in brackets; Male, percentage of male patients in %; $^{\Theta}$, only the allelic OR could be calculated for this study; - , data not provided in the article;

- AA: OR = 4.00, 95%CI = 1.26-12.65, P = 0.02
- AG: OR = 3.45, 95%CI = 1.13-10.58, P = 0.03

Jongepier et al 2005 [223] analysed a Dutch cohort of 200 asthmatic patients and their spouses. The participants were considered to suffer from atopic eczema if they reported having eczema in a questionnaire. As a consequence, both cases and controls involved asthmatics and their spouses which seemed to be an insufficient case-control design for the meta-analysis. For completeness, no significant association of Lys420 with atopic eczema was detected in this setting.

Studies included in the meta-analysis. Finally, a total of seven independent cohorts from five case-control studies with 3829 cases and 11646 controls were included in the meta-analysis. As most studies provided data on heterozygous genotypes versus wild-types only, this model was chosen for the pooled analysis by way of exception.

Table 3.1 provides characteristics of the studies like leading author, year of publication, country and ethnicity, numbers of patients and controls, allelic distributions, mean age of participants and percentage of male participants.

Regarding ancestry only two studies had been carried out on Asian populations, one in Japan and one in Korea. The remaining studies were performed on Europeans from Germany, France, Ireland and the United Kingdom. No additional samples from other than Asian or European descent were identified.

The mean age of participants ranged from 3.5 years to 28.7 years. There were studies on adults only and studies on children only, but most samples involved subjects of all ages. The male/female ratio between patients and controls was well balanced in most

study samples. Only the control group of Hubiche et al 2007 [198] comprised exclusively male participants.

Results of the meta-analysis. The results of the meta-analysis of the heterozygous SPINK5 rs2303067 (Glu420Lys) genotype and atopic eczema are summarized in Figure 3.4. As the Cochran Q test revealed no significant deviation from the homogeneity assumption (P = 0.2653), a fixed effects model was applied to calculate the estimated odds ratio. The outcome does not indicate an association between the genetic variant in question and atopic eczema (OR = 0.99, 95%CI = 0.90-1.10, P = 9.06E-01). The funnel plot analysis provides a symmetrical shape (Figure 3.5) and Egger's regression test did not indicate publication bias either (P = 0.2626).

The only significant study by Kato et al 2003 [233] was conducted on a Japanese cohort, implying a population specific association. Yet a study on another Asian population from Korea by Namkung et al 2010 [326] did not show a significant result, arguing against the hypothesis of a distinct pattern of inheritance across ethnicities. In addition, the frequency of the A allele did not differ considerably between Asian (56.1%) and European (58.0%) control populations. Neither the age of participants nor the male/female ratio seemed to have an influence on the outcome of the meta-analysis.

Discussion of the meta-analysis. The present meta-analysis was not able to confirm a significant association of the heterozygous SPINK5 rs2303067 (Glu420Lys) genotype with atopic eczema. The findings by Walley et al 2001 [508] in a UK family cohort had been replicated, but all studies with significant outcomes had to be excluded from the meta-analyses except for the study by Kato et al 2003 [233]. For European populations, Weidinger et al 2008 [518] described a weak effect for maternal transmission in German families and Kabesch et al 2004 [224] a significant association with German asthma patients with eczema, but not for eczema alone. In contrast, there were a number of replications for Asian populations indicating a dependency on ethnic origin.

All studies on Japanese subjects showed positive reports: First, the family of study Nishio et al 2003 [337] found a preferential transmission of Lys420 alleles to offspring with atopic eczema, then the study of Kusunoki et al 2005 [261] described an association of the polymorphism with disease severity in children with atopic eczema and finally the case-control study of Kato et al 2003 [233] confirmed these findings. The study by Namkung et al 2010 [326] on Korean subjects, however, could not establish a comparable result. Hence more studies will be needed to establish an association of the SPINK5 variant rs2303067 (Glu420Lys) with Asian populations.

In spite of the insignificant result of the meta-analysis which may partly result from the exclusion of several positive reports, mutations in the SPINK5 gene might show a functional relevance. The gene product is a serine protease inhibitor named LEKTI with a suspected immunosuppressive function and contribution to skin barrier function. Thus, a malfunction due to missense mutations might contribute to the development of atopic eczema. [85, 508]

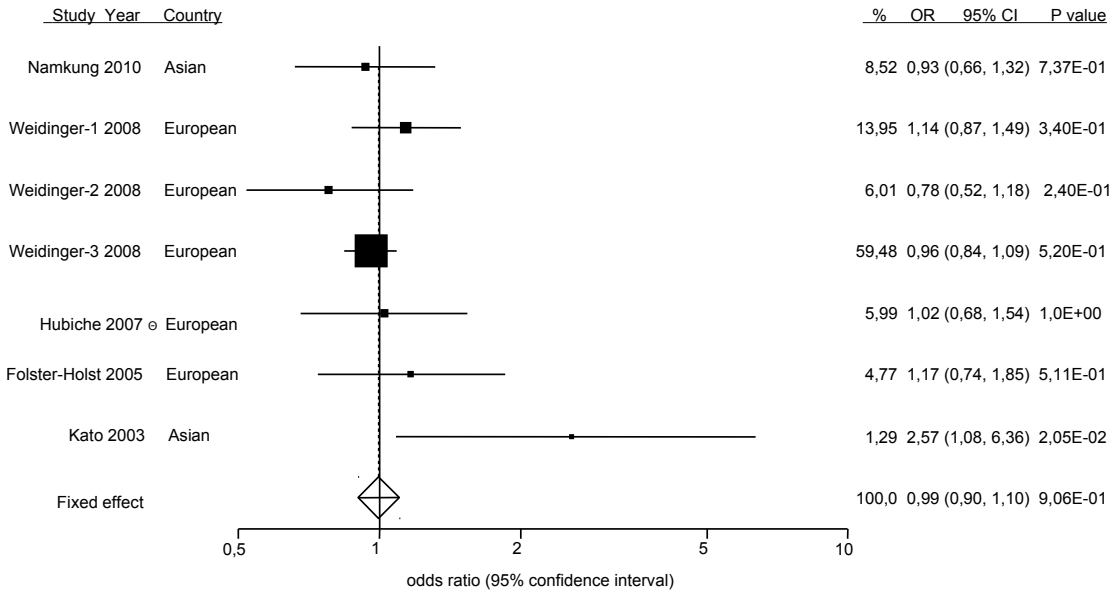


Figure 3.4.: Association of the heterozygous SPINK5 rs2303067 genotype with atopic eczema. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and ethnicity) included in the meta-analysis. %, weight; $^{\Theta}$, see Table 3.1.

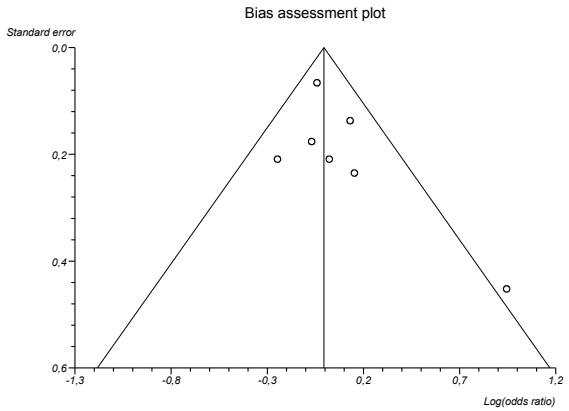


Figure 3.5.: Funnel plot showing log(OR)s and standard errors for the association of heterozygous SPINK5 rs2303067 genotype with increased risk for atopic eczema. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.2626.

3.2.2. CMA1 variant -1903G (BstXI)

The CMA1 gene on 14q11.2 encodes a serine protease secreted by skin mast cells. This so called mast-cell chymase is of functional relevance as it is involved in allergic and atopic inflammation of the skin [301]. For this reason allelic polymorphisms in CMA1 could be organ-specific genetic risk factors for atopy (see section 3.1.2).

Mao et al 1996 [301] found a significant association between the -1903 G allele, also referred to as rs1800875 or BstXI site, and atopic eczema in a Japanese cohort. Thereafter, a number of replication studies were performed, accumulating sufficient data to carry out a comprehensive meta-analysis.

Studies excluded from the meta-analysis. Three studies could not be included in the overall analysis as they investigated family data. Forrest et al 1999 [139] performed a TDT analysis on 46 trios from the United Kingdom, not achieving evidence for association between CMA1 BstXI polymorphism and atopic eczema.

Kawashima et al 1998 [235] performed a so-called haplotype-based haplotype relative-risk (HHRR) analysis in 69 patient-parents trios, showing no significant over-transmission of the BstXI B allele. An additional case-control sample confirmed this result and was included in the meta-analysis.

Iwanaga et al 2004 [215] investigated asthma families which suffered from additional eczema in 50% of the cases. In this setting, no significant over-transmissions were observed. An additional analysis of asthmatic parents with eczema compared to a control sample was included in the meta-analysis.

Concerning studies with case-control design, there were a total of seven publications on the association between CMA1 BstXI polymorphism and atopic eczema. The study of Mao et al 1998 [300] had to be excluded from the meta-analysis, however, due to insufficient genotyping data. They reported a significant association between atopic eczema and the heterozygous BstXI site in 145 Japanese patients and 696 controls.

Studies included in the meta-analysis. The remaining six case-control studies fulfilled the inclusion criteria, resulting in 771 cases and 2210 controls for the meta-analysis. Some characteristics of the studies are summarized in Table 3.2, showing the extracted data including name of the leading author, year of publication, country and ethnicity, numbers of patients and controls, allelic distributions, mean age of participants and percentage of male participants.

The diagnosis of atopic eczema was based on the criteria of Hanifin and Rajka in all but one of the studies. Iwanaga et al 2004 [215] on the contrary, used asthmatic subjects which reported to have had additional eczema at any time in their life. As a consequence, these results could represent an association with asthma as well as an association with any form of eczema and thus have to be treated with caution.

Concerning ethnicity, half of the investigations were based on Asian populations, all of them from Japan. The other half analysed European subjects from Italy, Germany and the United Kingdom. No additional samples from other than Asian or European descent were identified.

Table 3.2.: Characteristics of studies included in meta-analysis of CMA1 -1903 G (BstXI) polymorphism in atopic eczema

		Numbers		Frequency		Mean Age (SD/range)		Male	
Study [Ref]	**Country**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**
Weidinger 2005 [523]	Germany (E)	242	1633	28.4	22.6	49.0 (13.5)		46.2	
Iwanaga 2004 [215]	UK (E)	90	176	25.6	20.0	-	42.3 (-)	-	47.0
Pascale 2001 [368]	Italy (E)	70	100	24.0	24.0	-	9.4 (5-15)	51.4	55.0
Tanaka 1999 [469]	Japan (A)	169	100	62.0	54.0	24 (12-39)	26 (14-38)	57.4	46.0
Kawashima 1998 [235]	Japan (A)	100	101	66.0	63.0	11.1 (4-38)	12.5 (12-13)	-	-
Mao 1996 [301]	Japan (A)	100	100	71.0	53.0	25 (8)	adults	-	-
Total		771	2210	46.2	39.4				

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Frequency, frequency of the homozygous CMA1 BstXI genotype in %; Mean age, mean age of patients with standard deviation or range in brackets; Male, percentage of male patients in %; - , data not provided in the article;

There was substantial variety between the study samples regarding mean age of participants. Three studies were conducted on adults only, one on children only and the two remaining study groups had a rather low mean age at enrollment. Wherever provided, the male/female ratio between patients and controls was well balanced in the study samples.

Results of the meta-analysis. The performed meta-analysis provided a pooled odds ratio of 1.37 (95% CI = 1.11-1.69, P = 0.0029), supporting a positive relation between the homozygous CMA1 BstXI site and atopic eczema. A fixed effects models was applied for calculations as no significant heterogeneity between the studies was detected by Cochran Q test (P = 0.694). The forest plot in Figure 3.6 visualizes the results of the meta-analysis, showing individual odds ratios and the combined estimate. Egger's regression test and funnel plot analysis did not show a deviation from the symmetry assumption (P = 0.8716), thus not indicating publication bias (Figure 3.7).

The frequency of the B allele differed considerably between Asian (56.7%) and European (22.2%) control populations. When meta-analyses were performed divided by ethnicity, however, no significant changes in pooled odds ratios were observed. European studies showed a marginally weaker effect (OR = 1.32, 95%CI = 1.01-1.72, P = 0.0413) than the studies on Asian subjects (OR = 1.47, 95%CI = 1.05-2.07, P = 0.0256). Neither the age of participants nor the male/female ratio seemed to have an influence on the outcome of the meta-analysis.

Discussion of the meta-analysis. The present meta-analysis supports a significant correlation between the homozygous CMA1 BstXI site and the development of atopic eczema. Yet the fact that only two out of six studies achieved significant (Mao et al 1996 [301]) or borderline significant (Weidinger et al 2005 [523]) results in the first place,

puts this outcome into perspective.

For instance, Mao et al 1996 [301] could have overestimated the effect, being the first study to investigate the association and showing a low case number. On the contrary, underestimation of the effect could be due to small sample sizes in the other studies, especially Iwanaga et al 2004 [215] and Pascale et al 2001 [368]. An additional source of error is the inclusion of asthmatic subjects with self-reported eczema in Iwanaga et al 2004 [215].

Yet the only study showing a higher power to detect moderate effects by Weidinger et al 2005 [523] achieved a borderline significant result. In addition, Tanaka et al 1999 [469] showed a significant result in a subgroup of 47 pure atopic eczema patients with elevated IgE levels >500 IU/ml.

Besides association studies, the relevance of CMA1 as a candidate gene for atopic eczema was investigated by other research protocols. For instance, expression analyses reported increased levels of mast cell chymase in chronic atopic eczema. Interestingly, no up-regulation was observed in psoriasis, indicating an important role for mast-cells and its product in atopic eczema only [21]. This was confirmed by another study which found chymase not to be a promoter of inflammation in psoriasis [169].

Mast cell chymase has also shown to be a potential stimulus of neoangiogenesis in the skin which in turn is required for epidermal hyperplasia [159]. Moreover, the promotion of eosinophil infiltration forms another possibility of how mast cell chymase participates in the pathogenesis of atopic eczema [478].

Concerning animal models, CMA1 showed an altered expression in canine atopic skin lesions [535] while mouse models proposed therapeutic effects of specific chymase inhibitors in atopic eczema [513, 212, 317, 475]. Finally, a review on therapeutic advances in atopic eczema in 2009 suggested chymase inhibitors as putative future medications [354].

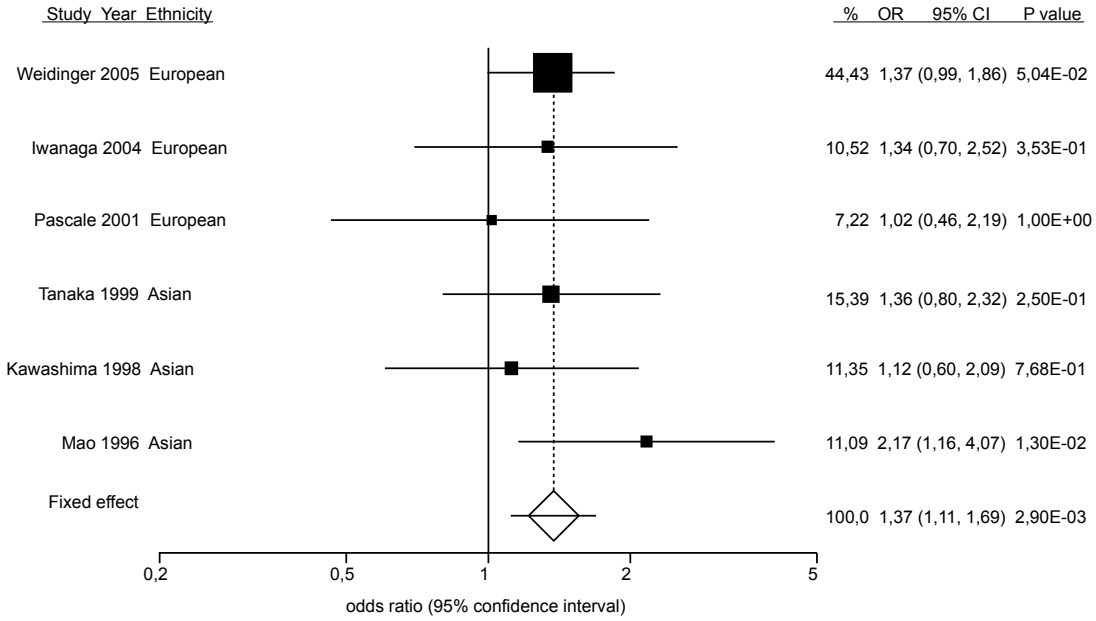


Figure 3.6.: Association of the homozygous CMA1 BstXI site with atopic eczema. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and ethnicity) included in the meta-analysis. %, weight.

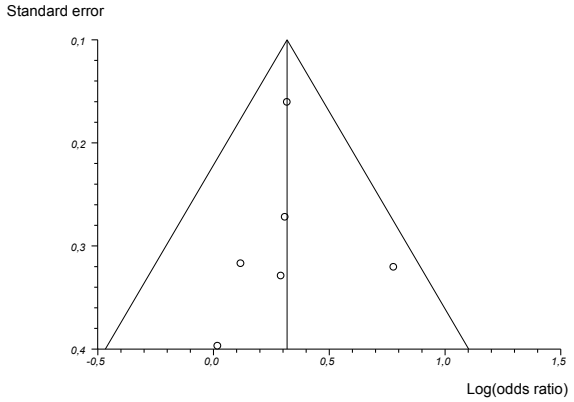


Figure 3.7.: Funnel plot showing log(OR)s and standard errors for the association of homozygous CMA1 BstXI site with atopic eczema. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.8716.

3.2.3. FLG variants R501X and 2282del4

The FLG gene is the undisputed number one risk gene for atopic eczema. As mentioned, the encoded protein forms part of the keratin cytoskeleton and its breakdown products are essential for water-binding in the epithelium (see section 3.1.2). That is why a malfunction results in a barrier dysfunction with an increased transepidermal allergen penetration and an elevated water loss. Genetic variants in the FLG gene are one way to impair the efficiency of this protein and by this the barrier function as observed in atopic eczema. As a consequence, there has been a lot of research in this area.

Findings of existing meta-analyses. Two of the most frequent FLG variants are R501X and 2282del4 null mutations. They have been analysed in family samples and case-control cohorts all over Europe and North America. In addition, two comprehensive meta-analyses summarizing the individual results were conducted. Baurecht et al 2007 [31] analysed eight case-control studies and four family studies from Germany, Austria, Denmark, France, UK, Ireland, Scotland and North America. They yielded high ORs for the FLG null alleles separately and the combined genotype of R501X and 2282del4 using a random effects model.

- R501X: OR = 3.51, 95%CI = 2.24-5.50
- 2282del4: OR = 3.62, 95%CI = 2.43-5.41
- combined: OR = 3.58, 95%CI = 2.43-5.26

These results stated FLG as the number one risk gene for atopic eczema. Interestingly, the association was lower in mainland European countries than in British and Irish cohorts. No Asian subjects were included in this meta-analysis.

Two years later, Rodriguez et al 2009 [400] included twice as many association studies in a second meta-analysis. In detail, 24 case-control studies including 5791 cases and 26454 controls and six family studies including 1951 families from Northern European countries and North America were pooled leading to similarly high association estimates.

- R501X: OR = 3.14, 95%CI = 2.45-4.03
- 2282del4: OR = 2.78, 95%CI = 2.28-3.39
- combined: OR = 3.12, 95%CI = 2.57-3.79

Again, a high risk was conferred by R501X and 2282del4 and their combined genotype in the overall analysis. The finding that allele frequencies and associations differed significantly between countries and ethnic groups was replicated. They concluded that the null polymorphisms R501X and 2282del4 are very common in European countries, but that Asian populations show a different spectrum of FLG variants. Since the publication of the meta-analyses, ten further association analyses on FLG have been published.

Findings of additional studies on European samples. A total of five new studies on polymorphisms in the FLG gene in sample sets from European background were identified. Most of them studied the common null mutations R501X and 2282del4 and a few included additional less frequent variants. For example, Bisgaard et al 2009 [41] tested a birth cohort of 411 children from Denmark and found that R501X and 2282del4 increased the risk of eczema in early childhood, by this replicating the findings of the previous meta-analyses.

Muller et al 2009 [316] conducted a family-based association analysis on subjects from 12 different European countries and Canada. They followed up 795 infants suffering from eczema with a positive family history. A transmission disequilibrium test yielded a highly significant association between both SNPs, separately and combined, with atopic eczema ($P < 0.0001$). No excess of maternal transmission was observed.

Stemmler et al 2009 [449] investigated a German case-control cohort consisting of 402 atopic eczema patients and 325 healthy controls. They were able to achieve a positive result for R501X and 2282del4 ($P = 0.0064$), but not for any other gene in the epidermal differentiation complex.

Another case-control study was performed by Gao et al 2009 [145]. A total of 278 European American patients and 257 controls were tested and for both the R501X and 2282del4 mutation a significant outcome was yielded ($P = 1.46E\text{-}05$ and $P = 3.87E\text{-}05$, respectively). In a subgroup of patients with additional eczema herpeticum, the association was even stronger. They replicated their findings in another cohort consisting of 188 African Americans with atopic eczema and 152 controls without signs for eczema. In this replication set, only the association with R501X remained significant ($P = 0.0351$).

O'Regan et al 2010 [356] studied 511 pediatric cases suffering from moderate to severe eczema and 1000 controls from Ireland. They found an association with the four most common FLG polymorphisms R501X, 2282del4, S3247X and R2447X (combined $OR = 5.81$, 95%CI = 4.51-7.49, $P = 1.26E\text{-}50$). In addition to that, they found rs7927894 in C11orf30 to be a genuine eczema susceptibility locus (Table A.1, p. 225).

In summary, one study using a birth cohort, one family study and two case-control studies evaluated R501X and 2282del4 and one additional case-control study analysed the combined genotype of R501X, 2282del4, S3247X and R2447X. All of these studies were performed on subjects with European ancestry and replicated the findings of the previous meta-analyses. A population of African Americans, on the contrary, seemed to be related to R501X only and not to the equally frequent 2282del4 polymorphism.

Findings of additional studies on Asian samples. In addition to the studies on subjects with European background, there were several studies on Asian populations as well. The initial publication on FLG variants in a non-European population was published by Nomura et al 2007 [343]. They genotyped 253 Japanese individuals for the R501X and 2282del4 null mutations at first and found that they were absent in this population. After that, they identified two new variants, S2554X and 3321delA, and conducted a case-control analysis on 143 Japanese patients with atopic eczema and 156 healthy controls. In this case, they found that S2554X and the combined genotype were associated

with an elevated disease risk.

One year later, Enomoto et al 2008 [126] conducted a case-control and family study on Japanese atopic eczema patients. They genotyped 96 patients for FLG mutations finding that both R501X and 2282del4 were not present in any of them. Other polymorphisms including S2554X and 3321delA were identified, however. While the analysis of 376 atopic eczema cases and 923 controls showed a significant association with S2554X (P = 0.0012), there was a non-significant over-transmission in 105 families. In addition, the 3321delA null allele was associated with elevated IgE levels and the combined genotype of S2554X and 3321delA with atopic eczema in both family and case-control samples (combined P = 0.00017). Furthermore, they found evidence of association with two additional variants, rs2065958 and rs12730241, in the family sample.

In the same year, Nomura et al 2008 [341] included 102 Japanese atopic eczema cases and 133 unrelated control subjects and genotyped them for S2554X and 3321delA and two further mutations S2889X and S3296X. The association reached statistical significance for the individual single nucleotid polymorphims S2554X, S2889X and S3296X and the combined genotype including 3321delA (P = 8.4E-07).

The same study group, Nomura et al 2009 [342], studied a combined genotype including seven FLG variants: R501X, 3321delA, S1695X, Q1701X, S2554X, S2889X and S3296X. They found that it was more frequent in 236 patients with atopic eczema than in 268 control subjects (OR = 6.8, 95%CI = 2.5-18.5, P = 1.75E-06). Approximately 25% of the patients carried at least one of the FLG mutations while only 4% of the controls did.

Another Asian sample was analysed by Ching et al 2009 [91], consisting of 174 Chinese children suffering from atopic eczema and 191 matched controls. They genotyped the sample for five FLG null alleles including R501X, 2282del4, R2447X, S2554X and S2889X. Only R501X was heterozygous in four male patients, that is to say 2.3% of all patients. The null mutation showed association with the long-term disease severity (P = 0.028), but not with the SCORAD index, age at onset or IgE levels.

The case-control study by Wang et al 2011 [510] was performed on a Taiwanese sample. A total of 116 children with atopic eczema and 212 controls were analysed for FLG polymorphisms. While R501X, 2282del4, S2554X, S2889X and S3296X were absent, the P478S GG genotype conferred an increased risk to develop atopic eczema in this sample (OR = 4.60, 95%CI = 1.19-11.24, P =0.002). After stratification by IgE levels, the association remained significant for children with IgE levels $\geq$100 kU/L only (OR = 5.67, 95%CI = 1.94-16.0, P < 0.05).

Ma et al 2010 [294] evaluated E2422X, Q2417X, S2554X, S2889X, S3296X, R4307X, 7945delA and 3321delA in another sample set from Northern China including 160 atopic eczema patients and 169 matched healthy controls. Only the latter polymorphism was identified, while the others were neither present in patients nor in controls. The analysis showed that 3321delA was strongly associated with the disease (OR = 2.54, 95%CI = 1.20-5.36, P =0.013), the heterozygous genotype being significantly more frequent in male patients, early-onset patients $\leq$ 2 years and patients with additional rhinitis and/or asthma.

In summary, three studies genotyped Asian samples for the common European FLG

mutations R501X and 2282del4. No association was identified and the mutations were even absent in all but one study which found the R501X null allele in four male patients. An association with 3321delA, however, was described in two Asian cohorts. While 3321delA alone was associated with Chinese patients, the combined genotype of 3321delA and S2554X was associated with Japanese patients. In addition, 3321delA was related to elevated IgE levels in the mentioned Japanese sample. Similarly, the P478S GG genotype was more frequent in Taiwanese patients with high IgE levels. Finally, a genotype including R501X, 3321delA, S1695X, Q1701X, S2554X, S2889X and S3296X was also related to atopic eczema in a Japanese study.

Discussion of existing meta-analyses and additional studies. The two common FLG variants R501X and 2282del4 have been established as major risk factors for atopic eczema in European populations. This was substantiated by two comprehensive meta-analyses and four additional candidate gene studies including case-control and family data. Yet the said variants seem to be common in individuals from European ancestry only. They were rare or absent in Asian and African populations.

In Japanese and Chinese cohorts FLG variants including 3321delA and S2554X have shown to be associated with atopic eczema, while they were not present in European populations [420]. This implies the existence of different FLG mutations depending on region and/or ethnicity. Consequently, every population could have their own set of mutations.

In addition to the results of candidate gene studies and meta-analyses, a genome-wide scan of Esparza-Gordillo et al 2009 [129] which was again based on a European population, found that the significantly associated marker SNP rs6661961 was in high linkage disequilibrium (LD) with the FLG null alleles at a distance of 156kb. As the association lost significance when excluding FLG mutation carriers, the effect seemed to depend on the FLG mutations and by this reflects the positive results of the meta-analyses.

3.3. Relevance of genetic predispositions to atopic eczema

As seen in the previous sections, levels of evidence for genetic predispositions can vary substantially. They range from single positive reports through replicated reports up to multi-stage genome-wide association studies and large meta-analyses. On the basis of this criterion, the candidate genes for atopic eczema can be rated according to their relevance.

Besides 90 candidate genes with exclusively negative reports (Table A.2, p. 230), the comprehensive *MEDLINE* search identified 65 genetic predispositions which had shown association with atopic eczema in at least one published study. Together with successful and unsuccessful replications, they are summed up in Table A.1 on page 225. In addition, the karyogram in Figure 3.8 provides an overview on the chromosomal locations of all candidate genes showing at least a single positive report. Yet more than half of them have not been replicated and thus may be false positive reports.

Twelve of these candidate genes obtained loose replications, in other words they were associated with atopic eczema in at least two independent cohorts but in deviating genetic variants. This was the case for some genes encoding interleukins or interleukin receptors like IL2 on chromosome 4q26-q27, IL7R on chromosome 5p13, IL5 on chromosome 5q31.1, IL4R on chromosome 16p12.1-p11.2 and IL12RB1 on chromosome 19p13.1.

Further genes with replications in deviating variants were NOD1 on chromosome 7p15-p14, TIMELESS on chromosome 12q12-q13 and CSF2 on chromosome 5q31.1. Interestingly, there were also loose replications for TSLP on chromosome 5q22.1 which enhances T cell recruitment in the pathogenesis of atopic eczema as well as for NOD2 on chromosome 16q21 which is involved in NF-κB signaling and DEFB1 which links innate and adaptive immune system and by this might play a critical role in the pathogenesis of atopic eczema. All of them were replicated in high-quality studies with an appropriate sample size of at least 100 subjects.

Another 17 candidate genes showed strict replications, in other words they were associated with atopic eczema in at least two independent cohorts and in the same genetic variant. All except two were replicated in studies which met some quality criteria as mentioned above. Both IL4 and TAP1 showed replications in studies with sample sizes below 100 subjects (Table A.1, p. 225). The locations of the remaining 15 genetic predispositions with strict replications are visualized and labeled in Figure 3.9.

Two of them have been discovered and replicated in sample sets of genome-wide association studies (GWAS), reaching a higher level of evidence due to large sample sizes and a hypothesis-free approach. These were C11orf30 on chromosome 11q13.5 and a single nucleotide polymorphism near HRNR on chromosome 1q21 which remained significant after stratification for common FLG null variants and thus represents an additional risk factor in the epidermal differentiation complex (EDC). They are marked by an asterisk in Figure 3.9.

In addition, some of the replicated candidate genes have been investigated by meta-analyses. In this case, the weight of a genetic predisposition can be evaluated by the

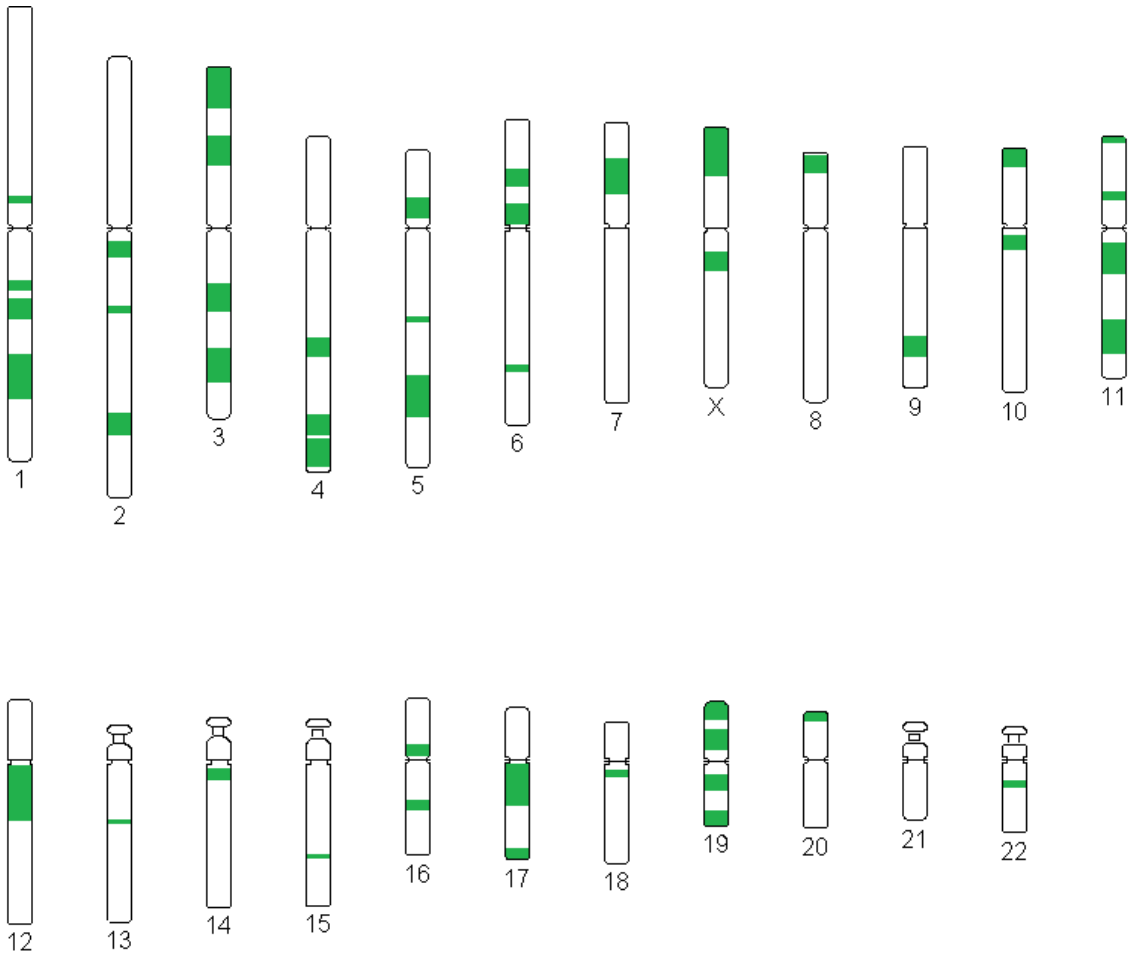


Figure 3.8.: Karyogram showing locations of genes with at least one positive report for atopic eczema.

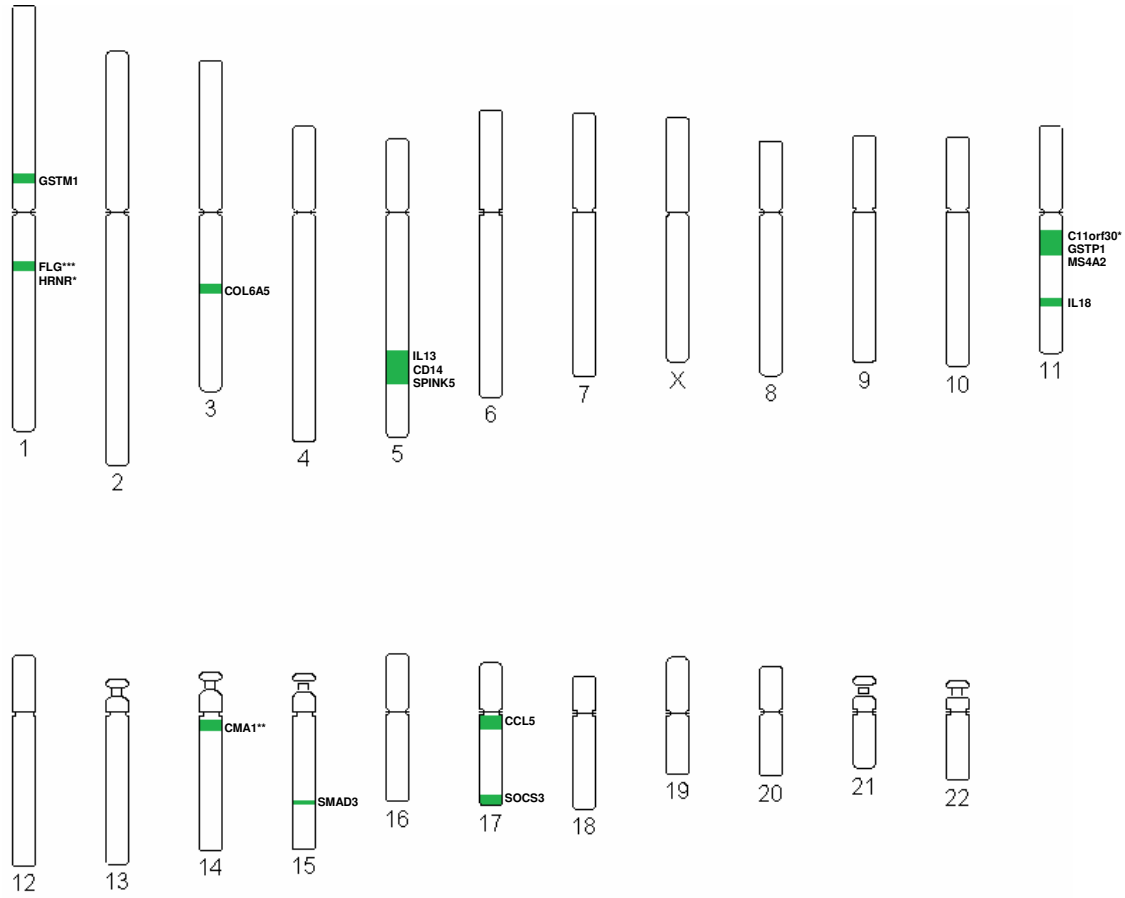


Figure 3.9.: Karyogram showing locations of genes with strict replications in high-quality studies for atopic eczema: *, affirmed by GWAS, **, affirmed by meta-analysis, ***, affirmed by both meta-analysis and GWAS.

association estimate achieved in the corresponding analysis. Yet for atopic eczema, only two meta-analyses could be added to the existing ones on FLG null mutations R501X and 2282del4. While the association with SPINK5 variant rs2303067 (Glu420Lys) did not reach statistical significance, the CMA1 variant -1903G (BstXI) showed a significant but lower estimate than the combined FLG variants R501X/2282del4 (Figure 3.10).

While CMA1 was affirmed by a meta-analysis only, FLG demonstrated significant associations in both a genome-wide association scan and two powerful meta-analyses, supporting its status as the major risk gene for atopic eczema. They were marked by two/three asterisks in Figure 3.9.

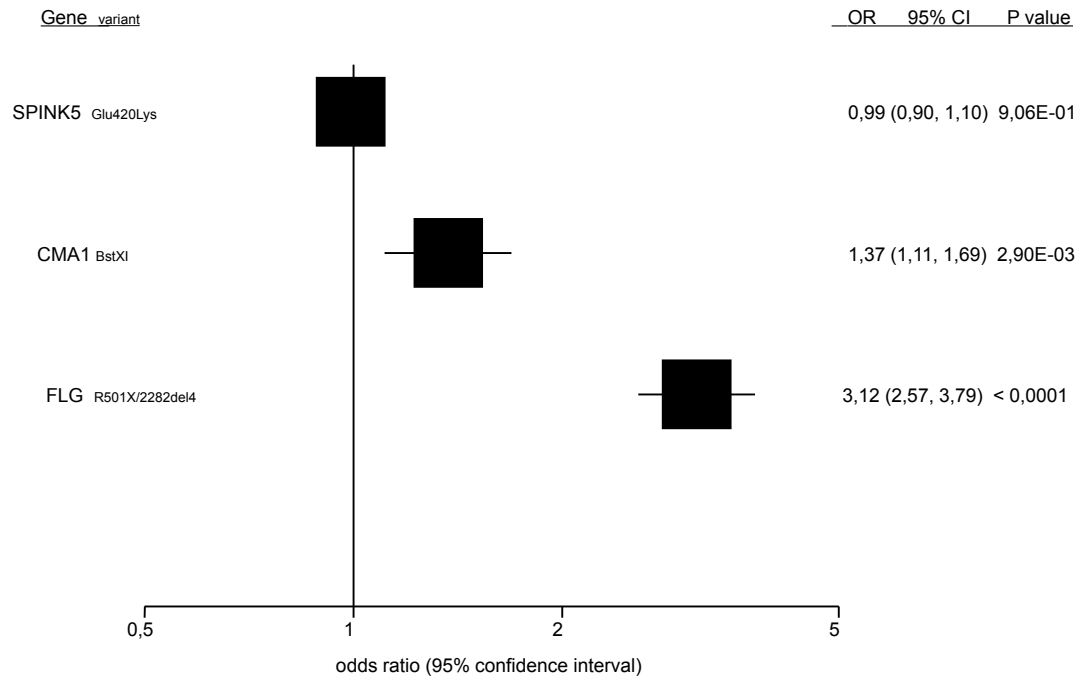


Figure 3.10.: Comparison of association estimates achieved in meta-analyses for atopic eczema, given by gene and variant. If two meta-analyses were performed for the same association, the larger was selected.

4. Genetic predispositions to psoriasis

Similar as for atopic eczema, it has become common knowledge that psoriasis is a complex disease with a multifactorial genesis. This is to say that both environmental and genetic factors contribute to the development of the disease. Especially a prevalence varying from region to region and within countries implies the involvement of environmental factors in disease expression. For instance, physical trauma or pressure can cause the development of psoriatic lesions (Koebner's phenomenon) as well as bacterial products by affecting epidermal cells.

The initial evidence of genetic factors underlying the development of psoriasis was provided by twin studies. Wuepper et al 1990 [539] reported concordance rates from the Stanford University database and the Danish twin registry. In both cases the concordance of psoriasis was higher in monozygotic (65%/72%) than in dizygotic twin pairs (15%/30%). Shortly afterwards, Duffy et al 1993 [116] analysed 94 Australian twins with confirmed psoriasis. Again monozygotic twin pairs were more often concordant for psoriasis than dizygotic twin pairs (35% vs. 12%), yielding a high grade of heredity of approximately 80%. There were no twin studies for psoriatic arthritis which might be due to its lower prevalence [383].

Chandran et al 2009 [72] analysed the recurrence risk of psoriasis and psoriatic arthritis in 100 Canadian patients and their first degree relatives. The estimated familial recurrence risk ratio was higher in psoriatic arthritis (30.4%) than in psoriasis without joint involvement (7.6%) implying specific risk variants.

For both psoriasis and psoriatic arthritis, a number of genetic predispositions have been discovered over the past decades. The corresponding levels of evidence vary, however, reaching from single positive reports through replicated reports up to multi-stage genome-wide association studies and robust meta-analyses. As a consequence, a comprehensive survey shall summarize all reports and their replications in order to give an overview on the current status of genetic research. In addition, meta-analyses on well-studied genetic variants shall be performed in order to validate individual reports.

4.1. Survey of genetic predispositions to psoriasis

In similarity to other hereditary diseases including atopic eczema, the genetic research on psoriasis passed through different stages using a number of different approaches. While twin studies promoted both heritable and environmental factors for the development of the diseases, genetic linkage analyses in families with atopic eczema proposed a couple of susceptibility loci. In total, twelve loci have been established for psoriasis and one additional locus for psoriatic arthritis. As said susceptibility loci can contain hundreds

of genetic variants they are usually examined in detail by fine-mapping in a second step. This in turn, can lead to the discovery of polymorphic candidate genes.

The analysis of pathogenic pathways is another way to identify candidate genes. The hypothesis that gene products play a role the pathogenesis of psoriasis is the idea of so-called candidate gene studies or association studies. As a consequence, genes encoding proteins involved in inflammation, immune response or skin barrier function are major candidates. Apart from their selection due to functional relevance, candidate genes can be derived from related diseases like for example Crohn's disease as well.

While candidate gene studies focus on a limited number of sites, genome-wide association studies (GWAS) are a more extensive way to identify genetic associations in the whole genome. As no previous knowledge on putative candidate genes is used, this approach is called "hypothesis-free". It has only been available for a few years now, but has already provided new insights.

In summary, all the discussed approaches lead to the identification of genetic predispositions to atopic eczema accumulating a large amount of data. In order to provide a comprehensive overview, the findings have been tabulated in a two-part survey. The first table involves all publications on genetic variants which have been associated with atopic eczema in at least one published study (Positive reports: Table B.1, p. 235) while the second table summarizes all genetic variants which have not shown evidence of association (Negative reports: Table B.2, p. 243). Genes with both positive and negative reports for different variants are marked with an asterisk.

In order to clarify the preparation of the survey, the strategies and findings of the different approaches will be discussed in more detail and striking results will be highlighted. First, susceptibility loci identified by genetic linkage analyses will be presented together with genetic predispositions mapping to them. Second, results of candidate gene studies will be described in exemplary form together with some background information. Third, genome-wide association scans and their findings will be discussed in order to complete the picture of genetic predispositions to atopic eczema.

4.1.1. Genetic linkage studies on psoriasis

As mentioned, genome-wide linkage analyses were carried out to establish susceptibility loci in the genome. For psoriasis, a total of twelve risk loci (PSORS1-12) have been discovered and one additional risk locus (PSORAS1) for psoriatic arthritis. As most of these linkage regions contain a high number of polymorphic genes, fine-mapping was used in order to locate promising candidate genes and variants.

Yet the replication of said susceptibility loci varies considerably. PSORS1, for instance, was detected in a number of individual linkage analyses while PSORS10 relies on a single published report. All loci except PSORS10 and PSORAS1 were analysed in detail by fine-mapping or in candidate gene studies.

In the following, the discovery and replication of the said psoriasis/psoriatic arthritis risk loci by genetic linkage analyses as well as the identification of candidate genes in these regions shall be discussed. Besides, Figure 4.1 provides an overview on the chromosomal locations of the discussed susceptibility loci.

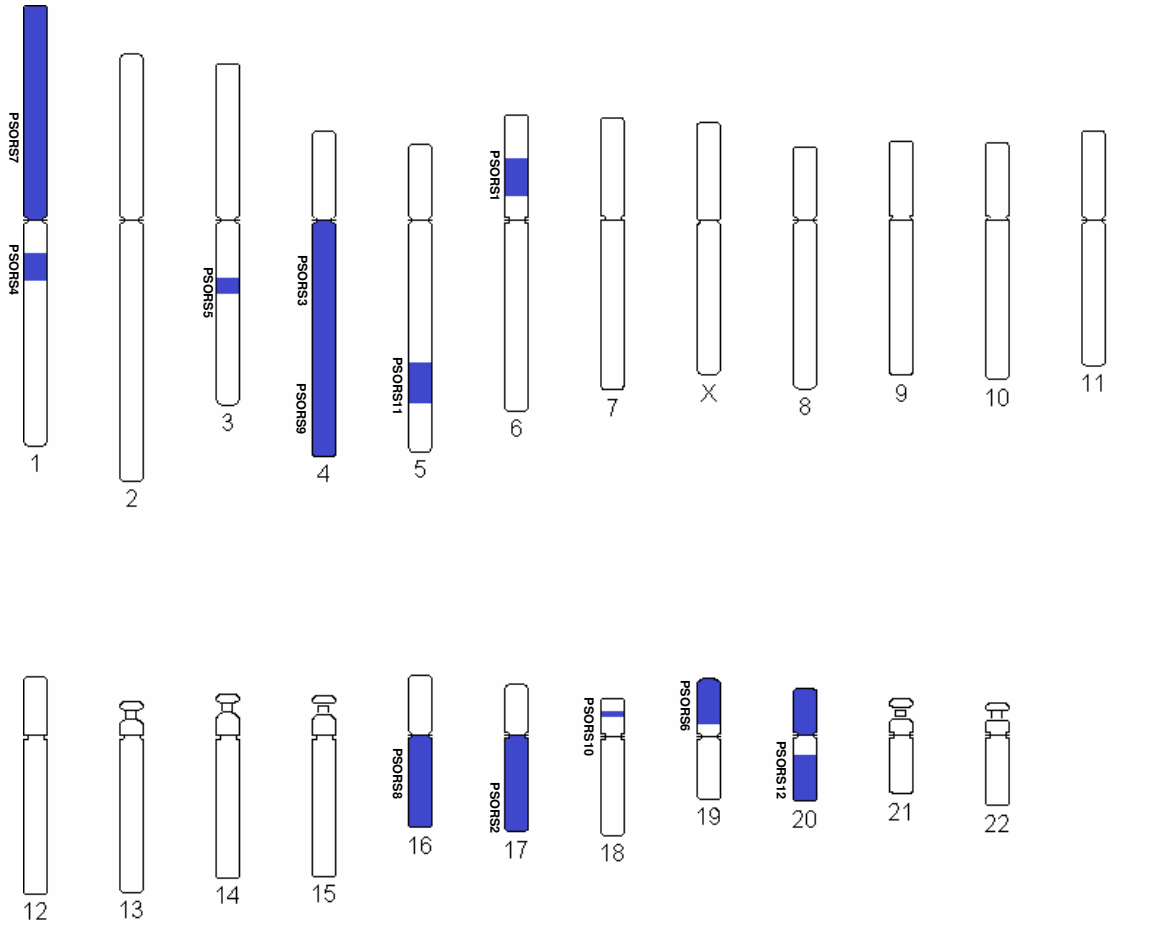


Figure 4.1.: Karyogram showing susceptibility loci for psoriasis established by linkage analyses; PSORS1-12.

PSORS1 (6p21)

A huge number of genome-wide linkage studies found an association between this locus on chromosome 6p21 containing the MHC gene cluster and psoriasis [480, 416, 319, 277, 274, 230, 556, 563, 504, 124]. Even a comprehensive meta-analysis involving six of these studies confirmed linkage to this locus [414].

In addition, HLA-antigens in this region had shown association to psoriasis back in the year 1972 [406]. While several fine-mapping studies excluded HLA-C in the first place [352, 321, 503, 357, 303], Nair et al 2006 [324] and Fan et al 2008 [130] supported the hypothesis of HLA-Cw*0602 being the major POSRS1 risk allele. The results of several genetic association studies on HLA-Cw*0602 and psoriasis were validated in a large meta-analysis (subsection 4.2.17). In addition, there was extensive research on the remaining HLA-Genes in the MHC cluster as well (Table 4.1) involving a meta-analysis on HLA-B*57 (see subsection 4.2.16).

Yet further PSORS1 candidate genes with positive associations should not be omitted from consideration (Table B.1, p. 235). Among them, CCHCR1, TNF, CDSN and MICA achieved the highest numbers of replications together with an intergenic SNP n.9 near HLA-C. As a consequence, meta-analyses were performed for all of them to validate their replications (see section 4.2).

Table 4.1.: HLA-Alleles in PSORS1 significantly associated with psoriasis in at least one published study.

HLA-Gene	HLA-Allele	Associations	References
HLA-A	*30	3	[284, 94, 20]
	*01	2	[284, 94]
	*0207, *24, *33	1	[94]
	*68	1	[20]
HLA-B	*57	META-ANALYSIS	[Table 4.22, p. 184]
	*13	3	[94, 20, 40]
	*27	2	[284]
	*40	2	[132]
	*7	1	[20]
	*8, *46	1	[94]
	*44	1	[40]
	*58	1	[284]
HLA-C	w*0602	META-ANALYSIS	[Table 4.25, p. 189]
	w*12	4	[284, 40, 132]
	w*7	2	[357, 6]
	w*1, w*4	1	[94]
	w*5	1	[357]
HLA-DRB1	*0701	6	[94, 20, 284, 218, 219]
	*1401	1	[218]
	*1502	1	[409]
	*17	1	[284]
HLA-DQB1	*0303	1	[219]
HLA-DQA1	*0501	2	[211, 218]
	*0201	1	[211]
HLA-DMA	*0101, *0102	1	[379]
HLA-DMB	*0103	1	[379]

HLA-Genes, given by their 'Official Gene Symbol' (aliases, gene name and location provided in the List of Genes; Associations, given by number of positive reports and corresponding references.

PSORS2 (17q)

A large number of linkage studies supported 17q as a susceptibility locus [477, 319, 124, 416, 563, 454, 230] while two scans were not able to replicate the finding [309, 150]. Yet one of them was carried out on psoriatic arthritis subjects indicating different linkage regions for this phenotype.

Later, Speckman et al 2003 [447] and Hwu et al 2005 [210] conducted fine-mapping analyses of the newly discovered locus. The former ascertained two candidate genes, CD300A and CD300LB, which showed single positive associations with psoriasis [447].

A subsequent study by Helms et al 2003 [176] reported two peaks in the linkage region. The first peak was indicated by marker SNPS within or between candidate genes NAT9 and SLC9A3R1 flanking a RUNX1-binding-site. All studies trying to replicate these polymorphic sites failed, however (Table B.1, p. 235). Filer et al 2009 [135] studied two other SNPs located in NAT9, but was not able to confirm an association with psoriatic arthritis either.

The other peak reported by Helms et al 2003 [176] involved three candidate genes named FDXR, GRIN2C and TMEM104. Five SNPs lying in or near these genes showed significant evidence of association in single positive reports (Table B.1, p. 235).

Another putative risk gene named RAPTOR involved two polymorphic sites which were associated with psoriasis in the study by Capon et al 2004 [66]. Here again, follow-up samples and replication studies were not able to confirm this finding [454, 150].

PSORS3 (4q)

Matthews et al 1996 [308] used 180 microsatellite markers to investigate putative candidate regions for psoriasis. One of these markers led to the q arm of chromosome 4 and was reproduced by further markers. Samuelsson et al 1999 [416] replicated this finding while Bahlerao and Bowcock 1998 [37] found linkage signals on chromosome 4q13-21. In addition, Karason et al 2005 [230] reached a significant LOD score for the locus in Icelandic families, highest for disease onset at or older than 17 years. Two further genome-wide linkage scans were not able to confirm the susceptibility locus on 4q [319, 124].

Several years later, a genome-wide association scan by Liu et al 2008 [287] mapped to SNPs within 4q26-27. Four polymorphisms between IL2 and IL21 were associated with psoriasis and psoriatic arthritis in two independent cohorts while another variant in IL2 had shown evidence of association in Korean patients with psoriasis earlier [244].

On chromosome 4q21, an insertion/deletion polymorphism in NFKB1 was tested in Chinese psoriasis vulgaris patients and matched controls by Li et al 2008 [280]. They found a significant association whereas Butt et al 2005 [58] were not able to replicate this finding in psoriatic arthritis subjects from Newfoundland.

The region between 4q31 and 4q34 is assigned to another psoriasis susceptibility locus named PSORS9 and will therefore be discussed there.

PSORS4 (1q21)

Two linkage genetic studies by Bahlerao and Bowcock 1998 [37] as well as Capon et al 1999 [67] established chromosome 1q21 including the epidermal differentiation complex (EDC) as a novel psoriasis susceptibility locus. Subsequently, Capon et al 2001 [68] narrowed the linkage region to an interval between markers D1S2346 and 140J1D by fine-mapping. Another refinement by Giardina et al 2004 [148] narrowed the interval to

about 100kb containing only a single gene named loricrin LOR. Yet they excluded LOR as psoriasis candidate gene because it lacked association in a subsequent Italian family sample. A marker SNP mapping to LOR in a later genome-wide association scan by Sun et al 2010 [458] was not associated either.

Genes belonging to the LCE cluster have since been major candidates instead. A comprehensive meta-analysis by Riveira-Munoz et al 2010 [399] supported the association of LCE3C/B deletion and the tagging SNP rs4112788 with psoriasis (see subsection 4.2.7) while another LCE3C/B polymorphism showed replicated association in a three-stage genome-wide association analysis by Zhang et al 2009 [557]. Moreover, there were positive reports for candidate genes LCE3A, LCE1A, LCE1C and LCE2A in the LCE cluster (Table B.1, p. 235).

Chen et al 2009 [86] discovered further candidate genes in the epidermal differentiation complex (EDC) on chromosome 1q21. Genetic polymorphisms lying within and between IVL, LELP1, PRR9, SMCP, SPRR2C, SPRR2F and SPRR2G showed single associations, but lack confirmation by an independent cohort. The same applies for variants in PGLYRP3 and PGLYRP4 [458, 226]. Similarly, S100 genes had shown significant over-expression in psoriatic lesions [553], but lacked evidence of association in candidate gene studies (Table B.2, p. 243).

Filaggrin (FLG), the major susceptibility gene for atopic eczema, was proposed for psoriasis as well. And indeed, two variants showed significant associations. While the risk allele at rs1858483 was over-transmitted in French families [360], the risk allele at rs11584340 showed a significantly higher frequency in Taiwanese cases compared to controls [74]. However, the genetic variants related to atopic eczema in European subjects, R501X and 2282del4, lacked evidence of simultaneous association with psoriasis in three independent cohorts [205, 560, 74].

PSORS5 (3q21)

A genome-wide linkage scan on Swedish families by Samuelsson et al 1999 [416] showed association of a microsatellite marker with chromosome 3q21, especially in patients with additional joint complaints. A subsequent pair-wise linkage study involving an extended set of Swedish families confirmed the susceptibility locus [125].

An association analysis by Samuelsson et al 2004 [417] was not able to establish CSTA or ZNF148 as PSORS5 candidate genes. In contrast, Vasilopoulos et al 2009 [495] reported an association of CSTA variant +162T/C with psoriasis a few years later. Meanwhile, intergenic variants were not associated [4].

Fine-mapping in Swedish families indicated SLC12A8 as a potential candidate gene [181]. It has since been tested in two association studies. First, Huffmeier et al 2005 [203] observed an over-transmission of one allele in German family data, while six different polymorphisms were significantly associated in case-control data. Second, Oudot et al 2009 [360] found evidence of association with two distinct variants in French families.

PSORS6 (19p13)

A genome-wide linkage study by Lee et al 2000 [274] using 370 microsatellite markers established 19p13 as a new psoriasis susceptibility locus. Nine years later, a further characterization of the locus was carried out by Huffmeier et al 2009 [201].

Both SMARCA4 and TYK2 lying in 19p13.2 were confirmed as psoriasis candidate genes in genome-wide association analyses. Nair et al 2009 [318] achieved a significant result for the SMARCA4 variant rs12983316 in two sample sets from Europe including 6407 affected subjects. Another two samples from the United Kingdom and Ireland comprising 6520 psoriasis patients, provided evidence of TYK2 polymorphisms rs12720356 and rs280519 [453].

PSORS7 (1p)

Veal et al 2001 [504] detected significant linkage signals on chromosome 1p with a non-parametric linkage score of 3.6 in 158 families from the United Kingdom. While the susceptibility locus was not reproduced in other genome-wide linkage scans, there were a number of positive reports by candidate gene studies (Table B.1, p. 235).

On chromosome 1p31.3, IL23R advanced to a major candidate gene for psoriasis over the last few years. It came into focus since the first genome-wide association analysis by Cargill et al 2007 [69] found an association with variants rs1120926 and rs7530511. The two polymorphisms have been studied extensively and meta-analyses were performed to validate the individual results (see subsection 4.2.10).

Centromeric on 1p31.1-p31.2, the genome-wide association scan by Liu et al 2008 [287] proposed a IL12RB2 variant, but there is lack of replication. The IL28RA polymorphism rs4649203 on 1p36.11, in contrast, has been replicated in a two-stage genome-wide association study by Strange et al 2010 [453].

Further centromeric on 1p13.3-p13.1, candidate gene PTPN22 was studied by means of meta-analysis (see subsection 4.2.3). In addition to that, GSTM1 and MTHFR showed single positive reports lacking replication (Table B.1, p. 235).

PSORS8 (16q)

Since Nair et al 1997 [319] had discovered this susceptibility locus on chromosome 16q, it was confirmed by subsequent linkage analyses including a scan on psoriatic arthritis subjects [231]. Stratification for joint involvement in a replication study indicated a pronounced linkage to psoriatic arthritis [230].

Relating to the identification of candidate genes, a gene named NOD2 was discovered on chromosome 16q21. The R702 variant showed over-transmission in a French family study [360] and significant association in a psoriatic arthritis case-control study [381]. In accordance with the results of linkage analyses, there was lack of association with skin-type psoriasis (Table B.1, p. 235).

CYLD on chromosome 16p12.1 showed a single positive report [360] while MMP2 on chromosome 16q13-q21 provided replicated evidence in distinct SNPs [501, 498]. In

contrast, there were merely negative reports for CX3CL1 on 16q13 as well as NQO1 on 16q22.1 (Table B.2, p. 243).

PSORS9 (4q31-34)

This psoriasis susceptibility locus was declared by Zhang et al 2002 [556]. A microsatellite marker mapped to 4q31 with a LOD score of 2.43 in 61 Chinese multiplex families while two markers in 4q28 did not indicate linkage. Two years later, a meta-analysis of six genome-wide linkage scans by Sagoo et al 2004 [414] supported a linkage region between 4q28 and 4q31.

A subsequent candidate gene study by Zhang et al 2007 [558] found g.96516A/T within the 3'-untranslated region of IL15 to be associated with Chinese psoriasis patients. Replication studies were not able to reproduce an association with this candidate gene though [283, 436, 516].

Bowcock et al 2004 [46] had proposed some candidate genes in this region including LRBA, TLR2, TLR3, VEGFC and IRF2. Merely VEGFC on chromosome 4q31.1-q34.3 and IRF2 on chromosome 4q31.1-q35.1 were tested in subsequent association studies, but without success (Table B.2, p. 243).

PSORS10 (18p11.23)

Asumalahti et al 2003 [18] searched for smaller susceptibility loci in Finnish families that lacked association to PSORS1. This led to the discovery of a linkage region on chromosome 18p with highest scores for 18p11.23, but there were no further reports on this susceptibility locus.

PSORS11 (5q31.1-q33.1)

There has been linkage to chromosome 5 in two independent genome-wide scans. In Samuelsson et al 1999 [416], D5S816 mapped to a linkage peak on 5q which was even more pronounced in a subgroup of patients with additional joint involvement. Meanwhile, Enlund et al 1999 [125] found association with microsatellite marker D3S436.

The first genome-wide association scan by Cargill et al 2007 [69] narrowed the candidate region to 5q31.1-q33.1. Polymorphisms in IL12B had shown significant associations and have since been investigated extensively. The results for rs3212227 and rs6887695 were summarized in meta-analyses (see subsection 4.2.9).

Another replicated candidate gene of this region is IL13, first tested by Chang et al 2007 [77]. The rs20541 variant was analysed in fourteen independent cohorts, most of them including psoriatic arthritis cases. Here, too, case-control data was sufficient to perform a meta-analysis (see subsection 4.2.8).

Polymorphisms within and between TNIP1 and ANXA6 were associated and replicated in genome-wide association studies as well. In addition to that, there were single positive reports for polymorphisms in candidate genes SLC22A4, SLC22A5, IL4, ADRB2 and IRGM (Table B.1, p. 235).

PSORS12 (20q13)

The first to describe a susceptibility locus on chromosome 20 were Trembath et al 1997 [480] and Nair et al 1997 [319]. Eleven years later Capon et al 2008 [64] confirmed this finding by a genome-wide association scan. They narrowed the locus down to a 47kb region spanning 20q13. The SNP rs495337, lying in the SPATA2 gene, showed significant association in an initial sample set and two replication samples. While Li et al 2009 did not confirm this finding, the genome-wide scan of Stuart et al 2010 [455] provided supporting evidence in two huge sample sets including 5895 psoriasis cases in total.

The initial analysis of Capon et al 2008 [64] found additional evidence for another SPATA2 polymorphism, two SLC9A8 polymorphisms and five RNF114 polymorphisms. One of these SNPs in RNF114, rs2235617, was replicated by the genome-wide scan of Strange et al 2010 [455].

The PI3 gene, also called SKALP/elafin gene, investigated by Kuijpers et al 1998 [259] did not show an association, neither to chronic plaque-type psoriasis nor to a pustular form of psoriasis.

PSORAS1 (16q)

Karason et al 2003 [231] defined a psoriatic arthritis susceptibility locus on chromosome 16q. Interestingly, this linkage region coincides with PSORS8 and includes the candidate gene NOD2 which has shown evidence of association with psoriatic arthritis [381].

Additional linkage regions

Some of the genome-wide linkage analyses allocated further candidate regions outside of established susceptibility loci. Especially chromosome 20p associated with marker D20S186 was replicated by Nair et al 1997 [319] and Trembath et al 1997 [480]. Subsequent studies established ADAM33 on 20p13 as a candidate gene for this additional linkage region [278].

4.1.2. Candidate gene studies on psoriasis

In this section, genes and genetic variants which have shown association with psoriasis in candidate gene studies shall be discussed in exemplary form. These putative susceptibility genes are characterized by both their location in the genome and the function of their gene products. As seen above, many genes have been investigated because they mapped to susceptibility loci described by genome-wide linkage studies. Another way of selecting candidate genes is to look at functional aspects which imply an involvement into the pathogenesis. Of course, there are genes which unify both the positional and the functional aspect. Apart from that, candidate genes can be selected due to an existing association in a related disease.

Candidate genes for psoriasis due to functional relevance

One very comprehensible reason for choosing candidate genes is the functional relevance. As the pathogenesis of psoriasis has become more and more uncovered during recent years, there is knowledge of important disease pathways and networks. The involvement in such a pathway or network implies a contribution to disease development. Hereby, genetic variants can lead to an up- or down-regulation of the gene product as well as a loss of function. Polymorphisms in regulatory regions might even control the expression of more than one gene.

To date, there are two mechanisms which are thought to be essential for the pathogenesis of psoriasis: a dysfunction of the skin barrier on the one hand and a dysregulated T cell response on the other hand. As a consequence, genes encoding structural proteins in the epithelium, immune mediators or other pro-inflammatory factors represent potential candidate genes.

Genes for epidermal differentiation. As an impaired epidermal differentiation contributes to the development of psoriasis, genes in the epidermal differentiation complex in PSORS4 on chromosome 1q21 are suitable candidates [74].

The two common FLG null mutations R501X and 2282del4 previously associated with atopic eczema, did not show association to psoriasis in three published studies (Table B.1, p. 235). Yet two other variants showed loose replication for FLG. While rs11584340 was significantly associated with 314 Taiwanese psoriasis patients [74], rs1858483 was over-transmitted in 126 French psoriasis families [360].

Further candidate genes in the epidermal differentiation complex are IVL, PGLYRP3 and PGLYRP4 as well as LCE genes and SPRR genes. Similar to filaggrin, the proteins encoded by these genes play an important role in cornification and the formation of the epidermal barrier [86]. And indeed, functional variants near IVL were associated with psoriasis, especially early-onset psoriasis, in a Singaporean cohort [86].

At the same time, PGLYRP3 and PGLYRP4 variants were over-transmitted in an American family sample, but this finding was not replicated in an independent case-control set [457]. Chen et al 2009 [86] found variants in SPRR genes to be associated with psoriasis patients from Singapore. Yet replication in a Finish cohort failed [226].

The most promising susceptibility region within the epidermal differentiation complex was the LCE cluster. There were positive reports for several LCE genes (Table B.1, p. 235). For example, two LCE3A variants were successfully replicated in three independent cohorts [557]. Furthermore, results for LCE3C_LCE3B deletion and tag SNP rs4112788 were outstanding. In addition to a number of association studies, both a multi-center analysis and a meta-analysis validated the association with psoriasis (see subsection 4.2.7).

Genes encoding glutathione S-transferases. As xenobiotic substances have been hypothesized to play a role in the development of psoriasis, genes encoding xenobiotic metabolizing enzymes like the so-called glutathione S-transferases are putative candidate genes [395]. Null mutations in both GSTM1 and GSTT1 have been investigated in

case-control studies. While the initial study by Reich et al 1999 [395] could not ascertain an association in a German cohort with early-onset psoriasis, a correlation was detected in a further German population of Richter-Hintz et al 2003 [396].

Antimicrobial human β-defensin genes. As antimicrobial activity and cytokine-like features are attributed to skin β-defensins, a critical role in the innate immune response and consequently in the pathogenesis of psoriasis can be hypothesized [340]. In addition, an expression-analysis showed very high concentrations of human β-defensins, especially hBD-2, in lesional psoriatic skin [168].

As a consequence, Hollox et al 2008 [193] genotyped Dutch and German case-control sets for a copy number polymorphism in the β-defensin-cluster on chromosome 8p23.1. They found that a higher genomic copy number of DEFB genes was significantly associated with psoriasis in both independent panels.

Genes linked with cytokines. That cytokines are involved in the pathogenesis of psoriasis is a long known fact. Interleukin-12, for example, induces the differentiation of adaptive immune cells to Th1 cells and interleukin-23 to Th17 cells [331]. A common p40 subunit of the said interleukins is encoded by the IL12B gene on chromosome 5q31.1-q33.1.

As it has influence on the balance between Th1 and Th2 cells, Tsunemi et al 2002 [486] suspected both a role in atopic eczema and psoriasis. They found that the IL12B rs3212227 (1188) A allele frequency was significantly decreased in 164 Japanese patients with atopic eczema, while it was significantly increased in 143 psoriasis patients.

Several years later, this finding was repeated for psoriasis in a genome-wide association analysis by Cargill et al 2007 [69]. Both rs3212227 and rs6887695 showed significant associations in a discovery sample and two replication sets. In total, over a dozen association studies were published and comprehensive meta-analyses were performed to confirm the results (see subsection 4.2.9).

In addition, genome-wide association scans identified further genes involved in interleukin-23 signaling like IL23R encoding part of the interleukin-23 receptor and IL23A encoding the p-19 subunit of interleukin 23 (see subsection 4.1.3). Especially the IL23R variants rs11209026 and rs7530511 demonstrated strong evidence of association in newly performed meta-analyses (see subsection 4.2.10).

In order to rule out associations of further cytokine gene polymorphisms with psoriasis, Chang et al 2007 [77] genotyped a Chinese cohort for IL1A, IL1B, IL1RN, IL4, IL8, IL10, IL13, TNF-α, TNF-β and IFN-γ. None of them showed a significant association.

Yet for IL1RN, IL10, IL13 and TNF-α there was a large number of subsequent positive reports so that meta-analyses were performed (see section 4.2). Only for IL19 there were not enough reports, but significant association was reported in patients with psoriasis and palmoplantar pustulosis from Estonia [248, 250].

The question whether genetic factors in the MIF gene encoding macrophage migration inhibitory factor play a role in the susceptibility to psoriasis, was investigated by Donn et al 2004 [112]. Polymorphisms -173G/C and -794CATT showed significant associations

in British case-control data and subsequently replicated in a Chinese cohort, where the former polymorphism only reached significance in late-onset patients.

Activating killer Ig-like receptor genes. Killer IgE-like receptors are found on the surface of natural killer cells which play a role in the maintenance of psoriasis. Together with HLA class I ligands they can either inhibit or activate the said cells. [302]

Research in a Canadian population showed that that individuals with activating KIR2DS1 and/or KIR2DS2/3 genes had a higher risk to develop psoriatic arthritis. Yet this held true only when HLA class I ligands for the homologous inhibitory KIR2DL1 and KIR2DL2/3 receptors were absent [302]. This was replicated for KIR2DS1 and psoriasis vulgaris in Japanese and Polish populations [460, 292].

Vascular endothelial growth factor gene. Endothelial cells express the vascular endothelial growth factor (VEGF) which is involved in the pathogenesis of psoriasis. It stimulates angiogenesis what brings about leaky blood vessels which in turn promote T cell migration. Polymorphisms in the VEGFA gene influence the expression of vascular endothelial growth factor in the skin. [331]

Subsequent association studies tested a number of coding VEGFA variants obtaining a number of positive (Table B.1, p. 235) and negative reports (Table B.2, p. 243). For the +405G/C polymorphism, strongest evidence was provided by an existing meta-analysis (see subsection 4.2.6).

Angiotensin converting enzyme gene. Angiotensin converting enzyme (ACE) is expressed in many different tissues like for example the skin and immune cells. Its biological effect is said to be proinflammatory and an essential role in functional activities of the skin is suspected [103]. In addition, it had been observed that treatment with angiotensin converting enzyme (ACE) inhibitors potentially induces or exacerbates psoriatic lesions [363].

Therefore Ozkur et al 2004 [363] tried to find out if genetic variants in the ACE gene increased the susceptibility to psoriasis as well. They genotyped 86 Turkish patients with psoriasis and 154 healthy controls for ACE insertion/deletion (I/D) polymorphism. There was no overall association, but the I allele was significantly more frequent in patients from psoriatic families and in patients with early-onset psoriasis. As a consequence, further association studies and a meta-analysis were performed to assess the role of ACE insertion in psoriasis (see subsection 4.2.5).

Vitamin D receptor gene. A long known treatment for psoriasis was the local application of vitamin D analogs like calcipotriol [252]. Consequently, it was assessed whether genetic variants in the vitamin D receptor VDR gene could be a marker of responsiveness. In the small study group of Kontula et al 1997 [252] allele frequencies did not differ significantly between responders (n=10) and non-responders (n=9).

Yet other family and case-control studies investigated the association of VDR restriction fragment length polymorphisms and psoriasis. While there were only negative

reports for FokI (Table B.2, p. 243), for other polymorphisms there was evidence of association in a sufficient number of studies to perform meta-analyses (see subsection 4.2.4).

Candidate genes for psoriasis derived from related diseases

Another way of selecting candidate genes is to look for reported associations in related traits. In the case of psoriasis these are predominantly inflammatory and autoimmune diseases. Genetic factors may influence common inflammatory pathways in the pathogenesis of multiple systemic inflammatory disorders [65]. This hypothesis was supported by an overlap of susceptibility loci in linkage analyses. For example, on chromosome 19p13 and 16q risk loci of psoriasis and Crohn's disease coincide [274, 319].

Association of NOD2/CARD15 and CDKAL1 with Crohn's disease. The chromosomal region on 16q contains a susceptibility gene for inflammatory bowel diseases like Crohn's disease: NOD2 (alias CARD15) [43]. As the susceptibility locus PSORS8 has been mapped to the same region by Nair et al 1997 [319] an association of NOD2 with autoimmune disorders in general was suspected. This hypothesis was substantiated by an increased life-time risk to develop psoriasis for patients with Crohn's disease [43].

The first attempt to confirm an association of NOD2 with psoriasis failed [322]. In contrast, further investigations showed replicated evidence for the R702W variant in psoriatic arthritis case-control data from Canada [381] and psoriasis family data from France [360]. Over-transmission was observed for additional polymorphisms in the French family trios while investigations of the R702W polymorphism did not reach statistical significance in further cohorts from Italy, Germany and the United Kingdom involving psoriasis with and without joint involvement (Table B.1, p. 235).

Variants lying in the CDKAL1 gene on chromosome 6p22.3 have been associated with Crohn's disease as well [53]. Even if the function of the gene product is not yet unraveled, a contribution to the autoimmune genesis of the disorder is suspected [530]. Subsequent candidate gene studies in other autoimmune diseases showed a correlation between the SNP rs6908425 and an increased incidence of psoriasis in two independent populations [530, 283].

Associations of PTPN22, ADAM33 and CTLA4 with diabetes mellitus type 1. Another example of a related autoimmune disease is diabetes mellitus type 1. For this disease, a replicated association with a single nucleotide polymorphism located in the PTPN22 gene on chromosome 1p13 was shown. As a generalized association with autoimmunity was suggested, the finding was tested in further traits like Grave's disease, systemic lupus erythematosus and rheumatoid arthritis [45].

Positive results substantiated the hypothesis and led to the investigation of PTPN22 variants in psoriasis. The best-studied variant, R620W, showed sufficient evidence of association to perform a meta-analysis including eight case-control cohorts (see subsection 4.2.3).

The ADAM33 gene on chromosome 20p13 encodes a disintegrin and metalloprotease. It was significantly associated with diabetes mellitus type 1 in families of European

descent [439] and before that with asthma [492]. Knowing this, Lesueur et al 2007 [278] tested 126 French psoriatic families for associations with ADAM33 polymorphisms.

They found that four SNPs involving rs597980, rs512625, rs677044 and rs44707 showed a significant over-transmission. For two of them replication was successful in independent samples sets. While rs597980 was replicated twice in North American populations [283], rs512625 was replicated by French case-control data [434]. One year later, Siroux et al 2008 [434] reported further association of another variant with early-onset psoriasis.

The cytotoxic T lymphocyte antigen 4 (CTLA4) gene on chromosome 2q33 was another candidate gene for common autoimmune diseases, as it plays an important regulatory role in the immune response. In detail, the antigen disables the co-stimulation of T-cells mediated by dendritic cells [47] and was associated with diabetes mellitus type 1, Grave's disease and autoimmune hypothyroidism suggesting a shared inflammatory pathway [491]. Yet an association with psoriasis could not be confirmed by six independent candidate gene studies (Table B.2, p. 243).

4.1.3. Genome-wide association studies on psoriasis

This hypothesis-free approach searching the entire genome for putative associations has been available for a few years now. For psoriasis, it has both replicated genetic predispositions established in candidate gene studies and added novel genetic risk factors. In some cases even replications in both European and Asian populations were available. To date, there have been a total of nine genome-wide association scans on psoriasis and one on psoriatic arthritis in particular (Table 4.2).

In the following, the genetic factors which were identified and/or supported by this approach will be discussed in exemplary form. They are listed according to functional relationships and the number of replications by independent genome-wide association studies (GWAS). Still, genetic variants found in single scans are usually replicated within the study by a number of independent sets providing high levels of evidence as well. All replicated findings are summarized in Figure 4.2 on page 71.

HLA-C. The genome-wide association scans showed high association estimates for MHC markers near HLA-C on 6p21.3. In detail, the HLA risk allele Cw*0602 was tested in the first study by Cargill et al 2007 [69] and showed a strong association to psoriasis in the discovery sample. This result was also included in a large meta-analysis of HLA-Cw*0602 later (see subsection 4.2.17).

The marker SNP rs12191877 located 13kb upstream to HLA-C was significantly associated in the genome-wide association studies of Nair et al 2009 [318] and Ellinghaus et al 2010 [120] as well as a follow-up study by Feng et al 2009 [132] including samples sets from Europe, North America and China.

Variant rs1265181, mapping 77kb to HLA-C, showed association in the discovery sample of the genome-wide association scan by Zhang et al 2009 [557] and two further replication samples [562, 561]. All samples were from Asian origin residing in China.

At 34.7kb upstream of HLA-C there was another marker for the MHC region referred to as rs10484554. It showed strong association with psoriasis in two scans by Liu et al

Table 4.2.: Characteristics of genome-wide association studies on psoriasis

					Numbers	
Study [Ref]	**SNPs**	**Sets**	**Country**	**Clinic**	**P**	**C**
Cargill 2007 [69]	25,215	Discovery	US (E)	PPA	467	500
		Replication 1	US (E)	PPA	498	498
		Replication 2	US (E)	PPA	481	424
Capon 2007 [65]	313,830	Discovery	UK (E)	P	318	288
		Replication 1	UK (E)	P	519	528
Capon 2008 [64]		Replication 2*	UK (E)	P1	1429	987
		Replication 3	Germany (E)	P	932	940
Liu 2008 [287]	311,398	Discovery	US (E)	PVA	223	519
		Replication 1	US (E)	PPA	577	737
		Replication 2	UK (E)	PA	567	480
Nair 2009 [318]	438,670	Discovery	Europe (E)	P	1409	1436
		Replication	Ger, US, Can (E)	P	5048	5041
Zhang 2009 [557]	620,901	Discovery**	China (A)	P	1139	1132
		Replication 1	China (A)	P	5182	6516
		Replication 2	China (A)	P	539	824
Sun 2010 [458]	494,902	Discovery	China (A)	P	8312	12919
		Replication 1	Ger, US (E)	P	3293	4188
		Replication 2	US (E)	P	254 families	
Ellinghaus 2010 [120]	2,339,118	Discovery	Germany (E)	PV	472	1146
		Replication	Ger, US, Can (E)	PV	2746	4140
Strange 2010 [453]	594,224	Discovery	UK, Ireland (E)	PV	2622	5667
		Replication	Europe (E)	P	3174	5464
Stuart 2010 [455]	2,502,313	Discoveries***	Europe (E)	P	1831	2546
		Replication	US, Can (E)	PV	4064	4685
Huffmeier 2010 [206]	1,585,307	Discovery	Germany (E)	PA	609	990
		Replication	Europe (E)	PA	1761	3727

Study, given by first author and year of publication; Ref, reference number; SNPs, number of SNPs tested in the genome-wide scan; Country, country where the study was carried out and descent of subjects given in brackets; E, European; A, Asian; Clinic, clinical psoriasis variants in patients; Numbers, numbers of patients and controls; P, patients; C, controls; *, overlap with Replication 1 sample of Capon 2007 [65]; **, the same sample was used in a follow-up study by Feng et al 2009 [132]; ***, combined discovery samples of Nair 2009 [318] and Ellinghaus 2010 [120]; P, psoriasis without further specification; P1, early-onset psoriasis (Type 1); PV, psoriasis vulgaris; PA, psoriatic arthritis; PPA, psoriasis without further specification and psoriatic arthritis; PVA, psoriasis vulgaris and psoriatic arthritis;

2008 [287] and Strange et al 2010 [453]. The samples sets involved subjects from the United Kingdom, Ireland and the United States.

Finally, rs3134792 centromeric of HLA-C was associated in the genome-wide association study by Capon et al 2007 [65] and rs13191343 upstream of HLA-C in Huffmeier et al 2010 [206], both including European samples.

In summary, all studies supported the MHC region as primary susceptibility locus and by this reflected the results of linkage analyses as well as candidate genes studies. However, only around 10% of individuals with variation in this genetic region develop psoriasis which indicates the presence of additional genetic factors [287].

ERAP1. Another two genome-wide scans lead to the discovery of an associated region on chromosome 5q15. The ERAP1 gene is located within this region and encodes the

so-called endoplasmic reticulum aminopeptidase 1. The said peptidase in turn trims peptide antigens to an optimal length for binding to MHC class I molecules like for example HLA-C [453, 458].

Strange et al 2010 [453] established an association of ERAP1 variant rs27524 with psoriasis in two European cohorts. At the same time, Sun et al 2010 [458] found SNP rs151823 to be associated with the said disease in four Chinese sample sets while a replication in populations from European descent was not successful.

IL12B and IL23R. The first genome-wide association scan by Cargill et al 2007 [69] revealed IL12B and IL23R as additional susceptibility determinants for psoriasis. The most significant marker was rs3212227 in the 3'UTR of IL12B located on 5q31.1-q33.1 which had already been suggested by Tsunemi et al 2002 [486].

In addition to rs3212227, significant associations were found for another IL12B variant, rs6887695, and two variants in the related gene Il23R on chromosome 1q31.3, rs7530511 and rs11209026. These four variants were replicated in several candidate gene studies and genome-wide scans by Capon et al 2007 [65] and Liu et al 2008 [287]. In addition, meta-analyses were performed on these individual results (see subsections 4.2.9 and 4.2.10).

For Il12B there were even a number of additional associations. For example, SNP rs7709212 was significantly associated in the studies of Capon et al 2007 [65] and Zhang et al 2009 [557] including samples sets from the United Kingdom and China.

Capon et al 2007 [65] found rs10045431 to be associated as well and Zhang et al 2009 [557] found that rs3213094 showed association with psoriasis in the Chinese cohort. The latter finding was replicated by the genome-wide scan of Strange et al 2010 [453] on European populations.

Further significant Il12B variants were rs2082412 in Nair et al 2009 [318] and rs2546890 as well as rs953861 in Ellinghaus et al 2010 [120]. Both were replicated in sample sets from Europe and North America.

For Il23R, there were reports on one further variant to be significantly associated with psoriasis. While rs2201841 was not detected by Capon et al 2007 [65] Nair et al 2009 [318] found an association. Two further Canadian case-control sample sets replicated this finding [384] while another family set from Finland did not [117].

In summary, all genome-wide association studies on psoriasis showed evidence of associations in IL12B and IL23R besides the MHC locus. By this, they support the results of early linkage analyses as Il12B is located within the PSORS11 risk locus on chromosome 5q31.1-q33.1 and IL23R within PSORS9 on chromosome 1q. In addition to that, both genes dispose of functional relevance in the pathogenesis of psoriasis [331].

IL23A and IL13. Two genome-wide associations scans by Nair et al 2009 [318] and Strange et al 2010 [453] showed significant association estimates for IL23A involved in IL-23 signaling like IL12B and IL23R as well as for IL13 involved in the modulation of Th2 immune responses. Both the IL23A variant rs2066808 and the IL13 variant rs20541 provided evidence of association with psoriasis in the said genome-wide associ-

ation analyses whereas the latter was replicated in additional case-control studies and a meta-analysis (see subsection 4.2.8).

While Nair et al 2009 [318] found another SNP located in IL23A, Cargill et al 2007 [69] had not been able to detect an association in this gene.

LCE-cluster. The first large genome-wide association study in a Chinese population by Zhang et al 2009 [557] identified a susceptibility locus in the LCE gene cluster on chromosome 1q21.3. They found significant associations for multiple SNPs located within the same linkage disequilibrium block including rs4085613, rs4845454, rs1886734 and rs4112788. The latter was replicated in two further genome-wide scans by Strange et al 2010 [453] and Ellinghaus et al 2010 [120].

The said SNP rs4112788 is located 584 nucleotides downstream of LCE3D and 4.5kb centromeric of LCE3C_LCE3B deletion. Both the single nucleotide polymorphism and LCE3C_LCE3B deletion have shown association with psoriasis in a number of additional candidate gene studies and a meta-analysis (see subsection 4.2.7).

The LCE1C variant rs6701216, in contrast, showed association in a genome-wide scan by Liu et al 2008 [287] but not in a case-control sample with psoriatic arthritis [48].

TNIP1, TNFAIP3, TRAF3IP2 and NFKBIA. The genome-wide association study by Nair et al 2009 [318] identified two genes that act downstream of TNF-α and regulate NF-κB signaling: TNIP1 and TNFAIP3. The TNIP1 variant rs17728338 on chromosome 5q32-q33.1 and the TNFAIP3 variant rs610604 on chromosome 6q23 were significantly associated in both the discovery cohort and the replication cohort from European descent.

The genome-wide scan of Strange et al 2010 [453] replicated the latter variant and found association for another variant in TNIP1, rs1023995. Here again, subjects from European countries or more precisely from the United Kingdom and Ireland were involved. Sun et al 2010 [458] investigated a Chines sample set, finding SNPs rs3762999 and rs999556 on 5q33.1 to be associated with psoriasis. These two polymorphisms are in linkage disequilibrium with both TNIP1 and ANXA6.

The TRAF3IP2 gene on 6q21 encodes the TRAF3 interacting protein 2, but it is also known as ACT1 encoding the NF-κB activator 1 protein [120]. An association of different variants was detected by three genome-wide scans so far. Huffmeier et al 2010 [206] found a significant association for rs13196377, rs13190932, rs13210247 and rs33980500 in their European sample set. The latter two SNPs were replicated in Ellinghaus et al 2010 [120] while Strange et al 2010 [453] discovered an association with rs240993 and rs458017 near TRAF3IP2.

The enzyme encoded by NFKBIA on chromosome 14q13 inhibits NF-κB signaling [455]. An association with different SNPs was discovered in three genome-wide scans by Strange et al 2010 [453], Ellinghaus et al 2010 [120] and Stuart et al 2010 [455] (Table B.1, p. 235). Yet the harboring PSMA6 is a potential candidate gene as well, as its gene product is involved in MHC class I antigen processing [455].

SPATA2-RNF114. A region on chromosome 20q13.1-q13.2 involving SPATA2 and RNF114 was reported as a susceptibility locus for psoriasis by Capon et al 2008 [64]. A number of SNPs showed evidence of association including rs2235617, rs1056198, rs6125829, rs2235616, rs636987, rs495337 and rs2769982. The highest combined p value was yielded for rs495337.

The association with this SNP was confirmed by Stuart et al 2010 [455], although not reaching genome-wide significance and a further replication by Li et al 2009 [283] failed. The rs2235617 variant, however, was detected by the genome-wide scan of Strange et al 2010 [453].

IFIH1. The genotyping data gained from the genome-wide association scan of Cargill et al 2007 [69] was further studied in Li et al 2010 [282]. By using additional markers they found significant associations with SNPs rs35667974 and rs10930046 on chromosome 2q24. The associated markers lie within IFIH1, the so-called interferon induced with helicase C domain 1 gene. The association with this gene which is involved in IFN-signaling was supported by Strange et al 2010 [453], although not in the same polymorphisms.

Additional associations. Some of the genome-wide association studies on psoriasis identified further genetic risk factors. For example, Liu et al 2008 [287] reported association signals within a number of susceptibility loci previously described in linkage analyses. A single nucleotide polymorphism within HCP5 (HLA complex P5 gene) on chromosome 6p21.3 (PSORS1) achieved very high association estimates independent from HLA-C.

Similarly, a SNP 4kb upstream from IL12RB2 showed association on chromosome 1p31.3-p31.2 (PSORS7) independent from the established risk gene IL23R and four polymorphisms between IL2 and IL21 mapped to chromosome 4q26-27 (PSORS3). In addition to that, there were significant associations between LHFP and COG6 on chromosome 13q13 and on chromosome 15q21 harboring ubiquitin-specific protease 8 and SPPLA2.

Strange et al 2010 [453] reported further association with a genomic locus on chromosome 1p36.11 harboring IL28RA, a cytokine receptor involved in IFN-signaling like IFIH1. Similarly, two chromosomal regions on 2p13-p12 and 19p13.2 map to REL and TYK2 involved in NFκB-signaling like NFKBIA. Interestingly, TYK2 lies within the susceptibility locus PSORS6 proposed by linkage analyses. A further marker mapped to an intergenic region on chromosome 3p24.

Finally, Stuart et al 2010 [455] found independent association signals in NOS2 on chromosome 17q11.2-q12 and FBXL19 on chromosome 16p11.2 while Sun et al 2010 [458] added susceptibility loci in PTTG1 on 5q35.1, CSMD1 on 8p23.2, GJB2 on 13q11-q12, SERPINB8 on 18q21.3 and ZNF816 on 19q13.41. Yet the latter loci were only significant in Chinese cohorts but not in replication samples from Germany and the United States.

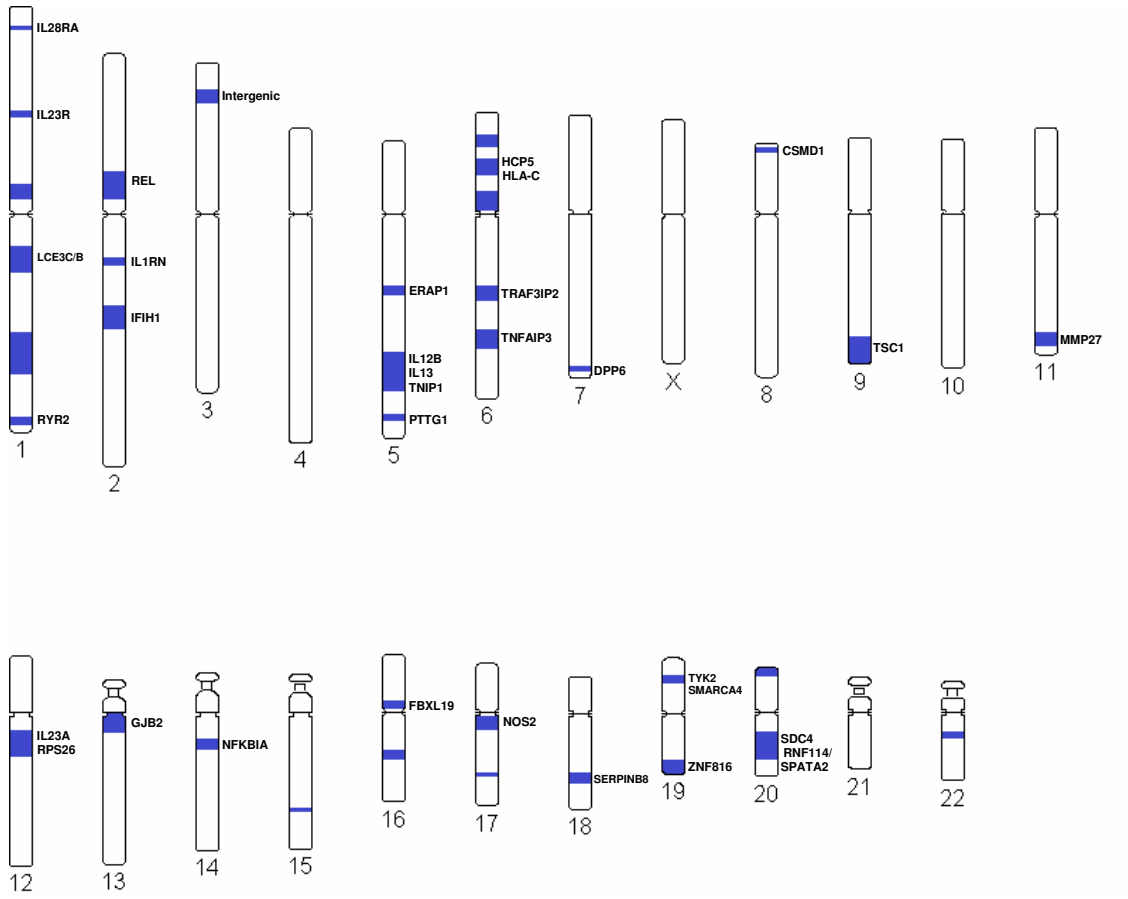


Figure 4.2.: Karyogram showing locations of genes with strict replications (in the same genetic variant) in high-quality studies for psoriasis. Those replicated by genome-wide association scans are labeled.

4.2. Meta-analyses of well-studied genetic variants for psoriasis

During the preparation of the survey, it became clear that some genetic variants had been analysed much more frequently than others. For these well-studied genetic variants, the performance of meta-analyses in order to validate the individual reports appeared to make sense. To achieve sensible results, a minimum number of six studies meeting the inclusion criteria was needed which was reached for 16 genes involving 15 single nucleotide polymorphisms, three haplotypes, three restriction fragment length polymorphisms, one variable number tandem repeat, one triplet repeat, one insertion and one deletion polymorphism.

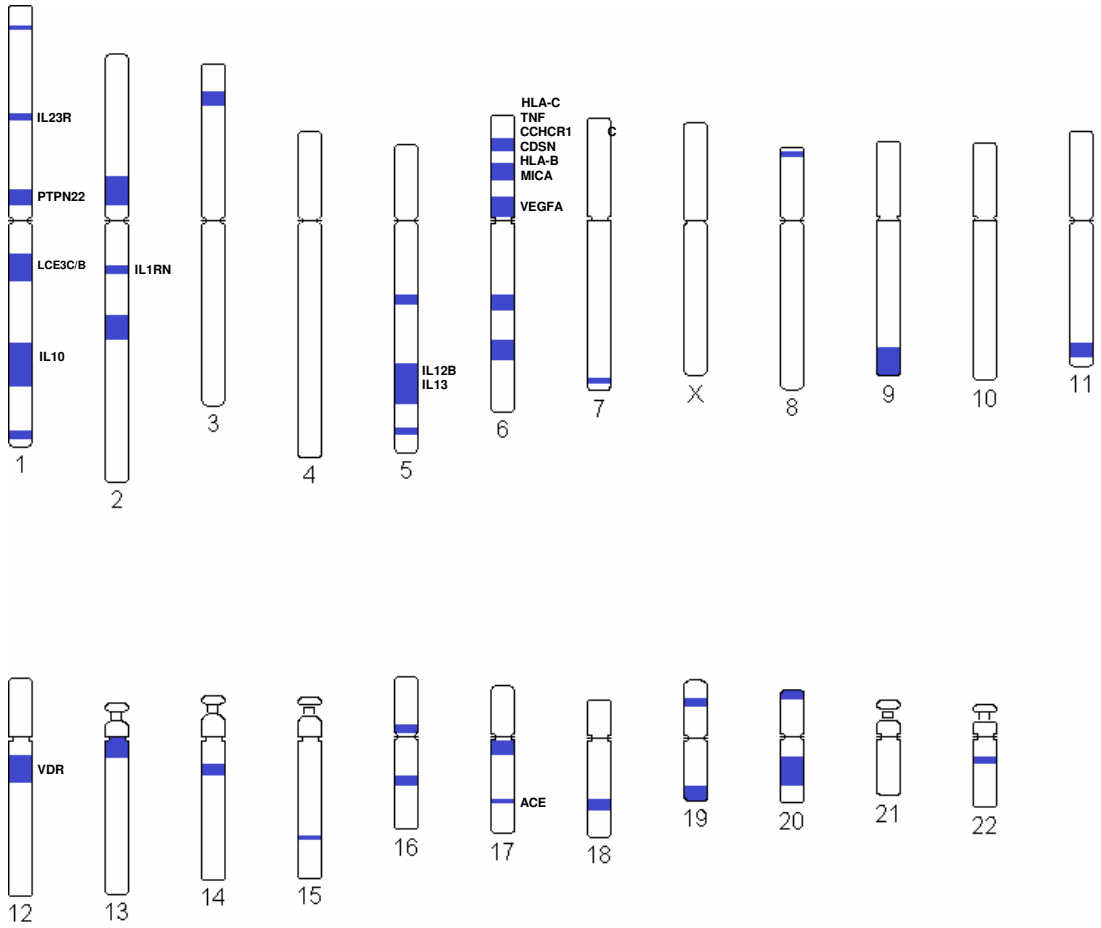


Figure 4.3.: Karyogram showing locations of genes with strict replications (in the same genetic variant) in high-quality studies for psoriasis. Those investigated by meta-analysis are labeled.

Figure 4.3 shows that more then one third of these well-studied genes are located in PSORS1 on chromosome 6p21.3 while another quarter can be found on chromosome 1 in susceptibility loci PSORS4 and PSORS7. Two more map to chromosome 5q31.1-q33.1 known as the PSORS11 locus while the remaining candidates lie outside established risk loci.

In the following, all meta-analyses on well-studied genes are listed according to their outcome. Investigations with negative results are followed by those with weak positive results and strong positive results. Newly performed meta-analyses are presented along with reports on existing meta-analyses.

4.2.1. IL1RN variable number tandem repeat

As cytokines in general are connected with the pathogenesis of psoriasis, genes dealing with interleukins represent putative candidates. This is the case for IL1RN which encodes an antagonist of the proinflammatory interleukin 1 [360]. It inhibits the binding to its natural receptor IL1R1 and by this leads to a loss of function. Based on this, a number of studies investigated the genetic variants of IL1RN and their association to autoimmune diseases like psoriasis (see section 4.1.2).

Oudot et al 2009 [360] reported a preferential transmission of the rs315934 A allele in French psoriasis family trios, while a genome-wide scan by Nair et al 2009 [360] discovered an association with SNP rs397211. The association was significantly replicated in a separate sample set, but although there was a positive tendency, the locus did not reach genome-wide significance.

A number of other association studies focused on the variable number tandem repeat (VNTR) in intron 2. Case-control data was provided by seven independent reports, enough to perform a meta-analysis.

Studies excluded from the meta-analysis. The study by Balding et al 2003 [24] genotyped 147 Irish psoriatic arthritis patients and 389 controls for cytokine polymorphisms including the IL1RN variable number tandem repeat. They found that frequencies did not differ significantly between the two groups, but did not provide genotyping data to implement their results. As a consequence the case-control study could not be included in the meta-analysis.

Studies included in the meta-analysis. The remaining studies met the inclusion criteria and thus six independent cohorts with 1046 cases and 1289 controls were included in the meta-analysis. Table 4.3 presents some characteristics of the studies like leading author, year of publication, country, clinical variant of psoriasis, numbers and variant allele frequencies of patients and controls, mean age at participation (with standard deviation or range) and percentage of male patients.

Concerning clinical psoriasis variant, there were two cohorts consisting of common psoriasis vulgaris cases. Two more studies analysed psoriatic arthritis samples and the remaining cohorts were not characterized concerning clinical subtype. All except one

Table 4.3.: Characteristics of studies included in meta-analysis of IL1RN VNTR in psoriasis

			Numbers		Frequency			
Study [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**Mean Age**	**Male**
Settin 2009 [429]	Egypt	P (37%)	46	98	15.2	21.1	46.7 (15-70)	30.4
Tarlow 1997 [470] $^{\Phi 1}$	UK/Ger (E)	P1	191	331	29.1	23.6	-	-
Tarlow 1997 [470] $^{\Phi 1}$	UK/Ger (E)	P2	80	331	15.0	23.6	-	-
Chang 2007 [77] $^{\Phi 2}$	Taiwan (A)	PV (49%)	170	210	5.6	7.4	52.1 (7-84)	72.4
Reich 2002 [392]	Germany (E)	PV (68%)	231	345	7.4	8.7	(11-92)	65.4
Chang 2007 [77] $^{\Phi 2}$	Taiwan (A)	PA (74%)	102	210	4.9	7.4	45.6 (19-79)	52.0
Peddle 2005 [370]	Canada (E)	PA	226	95	27.0	24.0	54.0	52.2
Total			1046	1289	14.9	15.4		

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Frequency, frequency of the IL1RN VNTR (2 repeats) in %; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Mean Age, mean age of patients with standard deviation or range in brackets; Male, percentage of male subjects in the patients group in %; P, psoriasis without further specification; P1, early-onset psoriasis (Type 1); P2, late-onset psoriasis (Type 2); PV, psoriasis vulgaris; PA, psoriatic arthritis; $^{\Phi 1-2}$, these studies use the same control subjects, respectively; - , data not provided in the article;

study provided percentages of early-onset psoriasis patients in the cohort. Tarlow et al 1997 [470] studied early-onset and late-onset psoriasis separately providing a direct comparison.

In terms of ethnic or geographic differences, it is noticeably that the analyses were carried out in various different countries. While the two cohorts of Chang et al 2007 [77] resided in Taiwan, Settin et al 2009 [429] studied subjects from Egypt. The samples of Tarlow et al 1997 [470] and Reich et al 2002 [392] were from European descent. The age distribution of the participants varied significantly as well, reaching from childhood to old age. In addition, the percentage of male patients reached from 72.4% to 30.4%.

Results of the meta-analysis. The results of the meta-analysis for the IL1RN variable number tandem repeat in intron 2 are visualized in Figure 4.4. Individual odds ratios for 2 repeats ranged from 0.57 to 1.33 and as Cochran Q test did not reveal a significant deviation from the homogeneity assumption (P = 0.0539), a fixed effects model was applied to calculate the pooled odds ratio. The outcome indicates a lack of association between the IL1RN variable number tandem repeat and psoriasis (OR = 0.97, 95%CI = 0.81-1.15, P = 0.702).

This is no surprise, however, as only the first case-control study by Tarlow et al 1997 [470] had detected a significant correlation in late-onset subjects (P = 0.019) and a borderline significant correlation in early-onset subjects (P = 0.055). In addition to that, significant publication bias was detected by Egger's regression test (P = 0.0239) while the funnel plot analysis shows an asymmetrical shape as well (Figure 4.5).

A dependence on age at onset might be argued as Tarlow et al 1997 [470] found

a more significant association in the late-onset form than the early-onset form. Yet this study was the only to differentiate between onset forms and to carry out a direct comparison. Settin et al 2009 [429] investigated mainly patients with late onset of the disease and achieved a non-significant result, which stands against the hypothesis of a onset-dependent association.

As Tarlow et al 1997 [470] did not specify the clinical psoriasis variant and all other studies did not show an association, a putative dependency of clinical subtype cannot be ruled out. Ethnic groups did not indicate different patterns of inheritance. Yet frequencies of the IL1RN variable number tandem repeat varied notably between studies, ranging from 7.4% to 24.0%. Still, this variability seemed to be independent from ethnicities (Table 4.3).

Discussion of the meta-analysis. The present meta-analysis did not support an association between the IL1RN variable number tandem repeat and psoriasis. This was not surprising, however, as only one out of six case-control studies had reported a significant association with late-onset psoriasis and a borderline significant association with early-onset psoriasis. In addition, this study by Tarlow et al 1997 [470] was the first to investigate the association between the IL1RN VNTR and psoriasis, what makes an overestimation of the effect conceivable.

In accordance with the result of the meta-analysis, the excluded study by Balding et al 2003 [24] had not found a significant association either. However, there were additional loose replications (in deviating genetic variants) of IL1RN as a candidate gene in a family cohort [360] and a genome-wide association scan [360]. In addition, an expression analysis reported elevated serum levels of interleukin 1 receptor antagonist in patients with psoriasis compared to healthy controls. The levels were independent from disease severity (PASI) and phototherapy, suggesting systemic inflammation [9].

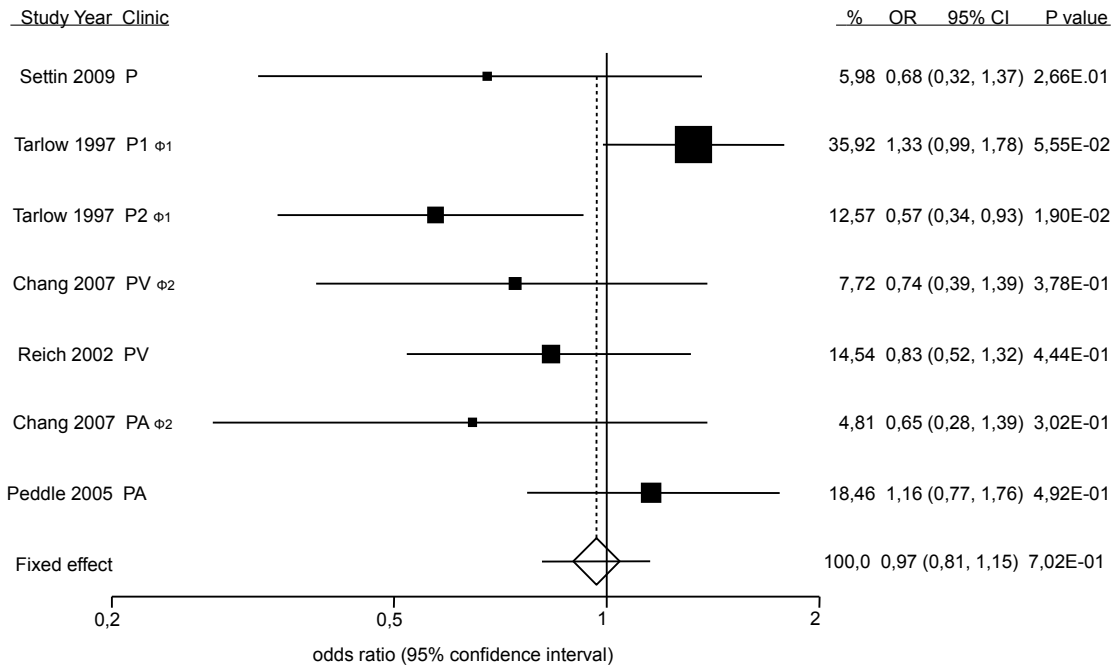


Figure 4.4.: Association of IL1RN VNTR (2 repeats) with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.3.

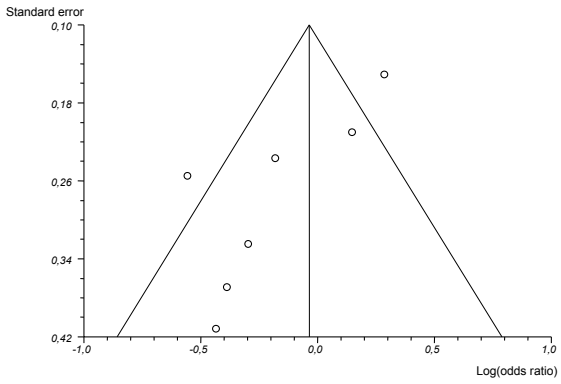


Figure 4.5.: Funnel plot showing log(OR)s and standard errors for the association of IL1RN VNTR (2 repeats) with psoriasis. Bias indicators showed significant deviation from the symmetry assumption, thus indicating publication bias: Egger's regression test P = 0.0239.

4.2.2. IL10 variant -1082G

As interleukins play an important role in inflammation, genetic variants in IL10 are putative candidates for susceptibility to chronic inflammatory skin diseases like psoriasis (see section 4.1.2). In addition, the gene is highly polymorphic and as a consequence several SNPs have been tested for association with psoriasis so far.

The variants -592C, -819C and -3575A lacked association (Table B.2, p. 243), while there were positive reports for -2763A and -1082G. However, there were only replication studies for the latter polymorphism, involving total of seven case-control cohorts. These data were sufficient to perform a meta-analysis on -1082G.

Studies excluded from the meta-analysis. As mentioned in the previous section, Balding et al 2003 [24] genotyped 147 Irish psoriatic arthritis patients and 389 controls for cytokine polymorphisms including not only the IL1RN variable number tandem repeat but also the IL10 -1082A variant. Here again, they found that frequencies did not differ significantly between cases and controls. As no genotyping data was provided in the article, the results had to be excluded from the meta-analysis.

The same applies to the study by Kim et al 2007 [244]. They investigated polymorphisms of IL-2, IL-4, IFN-γ and IL-10 in 114 psoriasis patients and 281 healthy controls from Korea. The frequency of the IL-10 -1082 G allele was similar in cases and controls, not indicating an association with psoriasis.

As significant associations were reported for the -1082 GG genotype [429] only, the meta-analysis was performed on the basis of genotype frequencies by way of exception. Consequently, two case-control studies had to be excluded because their genotype frequencies were too low. In a psoriatic arthritis sample by Chang et al 2007 [77] there was no patient with a GG genotype while there was no control subject with the GG genotype in the study by Wongpiyabovorn et al 2007 [533]. Both studies did not indicate an association for the -1082 G allele.

Further studies included -1082 into haplotype-analyses. Al-Heresh et al 2002 [3] was the first to analyse the (-1082, -819, -592) haplotype in 124 psoriatic arthritis patients and 101 controls from the United Kingdom. No difference in the distribution of the haplotype was found. One year later Kingo et al 2003 [247] replicated this finding in 248 Estonian psoriasis cases and 148 controls. Still, they postulated a disease-modifying influence of the IL10 haplotype as patients with low PASI scores, low extent and persistent course of the disease showed a significant association.

Baran et al 2008 [28] started another attempt to bring light into the dark of IL10 haplotype association. Again no statistically significant differences in haplotype frequencies were found between 78 Polish psoriasis patients and 74 controls. A dependency of disease-onset was considered non-significant after Bonferroni correction for multiple testing. Another haplotype (-3575, -2763, -1082, -592) investigated by Wongpiyabovorn et al 2007 [533] did not show association either. Yet the AAGC haplotype frequency was significantly increased in late- compared to early-onset psoriasis.

Table 4.4.: Characteristics of studies included in meta-analysis of IL10 -1082 GG genotype in psoriasis

			Numbers		Freq			
Study [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**Mean Age**	**Male**
Settin 2009 [429]	Egypt	P (37%)	46	98	50.0	47.4	46.7 (15-70)	30.4
Craven 2001 [106] $^{\Phi 1}$	UK (E)	P1	47	330	50.0	50.9	-	41.7
Craven 2001 [106] $^{\Phi 1}$	UK (E)	P2	31	330	46.8	50.9	-	41.7
Reich 1999 [395] $^{\Phi 2}$	UK (E)	PV1	100	123	50.0	49.2	(11-92)	63.6
Reich 1999 [395] $^{\Phi 2}$	UK (E)	PV2	51	123	45.1	49.2	(11-92)	63.6
Chang 2007 [77]	Taiwan (A)	PV (49%)	170	210	5.6	7.4	52.1 (7-84)	72.4
Peddle 2005 [370]	Canada (E)	PA	226	95	53.0	51.0	54.0	52.2
Total			671	856	42.9	41.2		

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Freq, frequency of the IL10 -1082 G allele in %; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Age, mean age of patients with standard deviation or range in brackets; Male, percentage of male patients in %; P, psoriasis without further specification; P1, early-onset psoriasis (Type 1); P2, late-onset psoriasis (Type 2); PV, psoriasis vulgaris; PV1, early-onset psoriasis vulgaris (Type 1); PV2, late-onset psoriasis vulgaris (Type 2); PA, psoriatic arthritis; $^{\Phi}$, these two studies use the same control subjects; - , data not provided in the article;

Studies included in the meta-analysis. As the remaining studies met the inclusion criteria, a meta-analysis was performed on seven independent cohorts with 671 cases and 856 controls. Table 4.4 presents some characteristics of the studies.

As mentioned, there were positive reports for the IL10 -1082 GG genotype [429] only but not for the G allele. Consequently, the meta-analysis was performed on the basis of genotype frequencies instead of allele frequencies by way of exception. Odds ratios were calculated for the GG genotype in relation to all the other genotypes (GA/AA).

Concerning the studies involved in the meta-analysis, several difference were observed. For instance, there were three cohorts consisting of common psoriasis vulgaris cases and one contained psoriatic arthritis cases. The remaining cohorts were not characterized concerning clinical subtype.

All except one study provided the distribution of onset types. While Settin et al 2009 [429] involved a higher number of late-onset subjects, the distribution was balanced in Chang 2007 [77]. Craven et al 2001 [106] and Reich et al 1999 [395] analysed early-onset psoriasis and late-onset psoriasis separately.

Relating to ethnicity, the subjects included in the meta-analysis were mainly from European descent. Craven et al 2001 [106] and Reich et al 1999 [395] studied subjects from the United Kingdom and Peddle et al 2005 [370] used a Canadian sample. The sample of Settin et al 2009 [429] was from Egypt while Chang et al 2007 [77] included participants residing in Taiwan. The age distribution of the participants reached from childhood or adolescence to old age and the percentage of male patients varied from

72.4% to 30.4% between studies.

Results of the meta-analysis. The results of the meta-analysis for the homozygous IL10 -1082 GG genotype are summarized in Figure 4.6. A recessive model was used as there were positive reports for this setting only and as Cochran Q test did not reveal a significant deviation from the homogeneity assumption (P = 0.2881), a fixed effects model was applied to calculate the pooled estimate. The meta-analysis indicates a lack of association between the IL10 -1082 GG genotype and psoriasis (OR = 1.09, 95%CI = 0.79-1.50, P = 0.614). No publication bias was detected via funnel plot analysis (Figure 4.7) nor by Egger's regression test (P = 0.9591).

Out of seven cohorts, there was one significant result by Settin et al 2009 [429] and one borderline significant result by the late-onset cohort of Craven et al 2001 [106]. These cohorts show several common characteristics. First, both show relatively small sample size with low numbers of cases in particular. Second, they involved either a high percentage of late-onset subjects or exclusively late-onset subjects. Third, the lowest percentages of male patients were observed in these samples (Table 4.4). Last, psoriasis phenotypes were not specified and thus the cohorts might include rare phenotypes different from the common forms psoriasis vulgaris and psoriatic arthritis.

Yet the association estimates of the two studies indicate deviating effects, one implies an increased risk to develop psoriasis and the other a decreased risk when carrying the GG genotype. As a consequence, the significant results do not seem to depend on disease onset, gender and clinical subtype, but are most likely explained by overestimation due to small sample sizes.

No differences in association estimates between samples from different ethnicities were observed either. Yet the allele frequencies of IL10 -1082G deviated significantly, being a lot less frequent in the Asian control population (7.4%) than in those from Europe or European descent (50.4%).

Discussion of the meta-analysis. The present meta-analysis did not support an association of the IL10 -1082 GG genotype with psoriasis. This agrees with the fact that all excluded association studies had shown negative results as well. The only two publications accounting for an association showed several common characteristics. They involved mainly or exclusively late-onset psoriasis, both did not specify the clinical psoriasis variant and the percentage of male patients was low. Yet the association estimates of the two studies indicate deviating effects. Therefore, overestimation due to small sample sizes is the most likely explanation for the significant results.

In conclusion, the relation of IL10 and psoriasis remains unclear. There were studies proposing an influence concerning disease severity, extent, course or onset [247, 533]. Thus a disease-modulating function seems more plausible than a contribution to disease susceptibility. Meanwhile, the role of interleukin 10 in the pathogenesis of psoriasis was investigated by different research protocols. Expression studies and immunohistochemical analyses found a relative IL10-deficiency and a low expression of interleukin 10 in psoriatic skin [14].

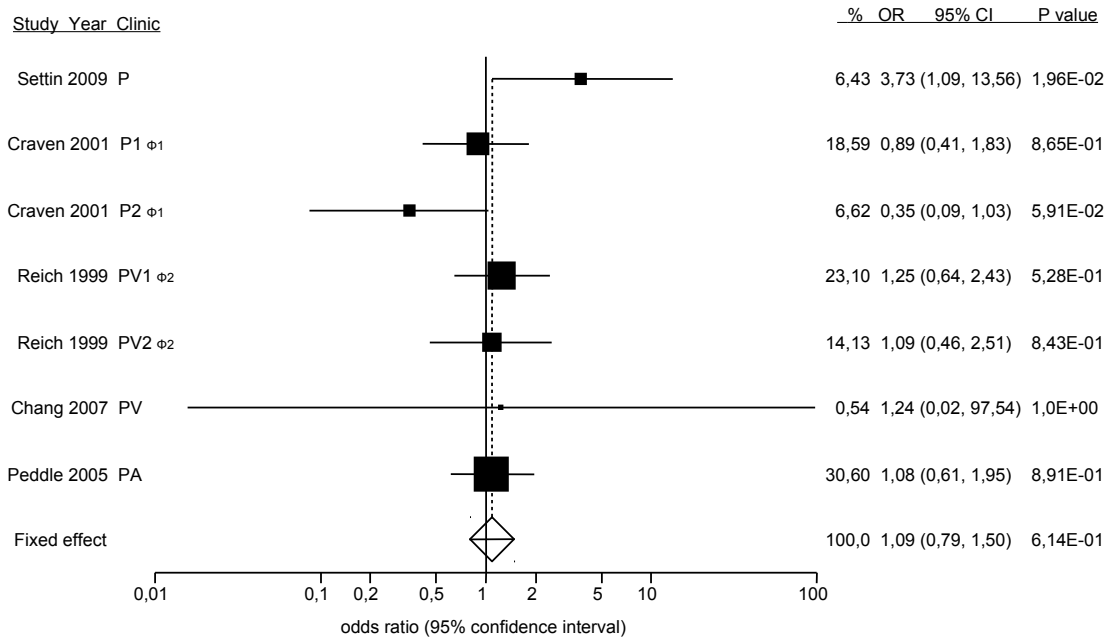


Figure 4.6.: Association of IL10 -1082 GG genotype with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight, abbreviations see Table 4.4.

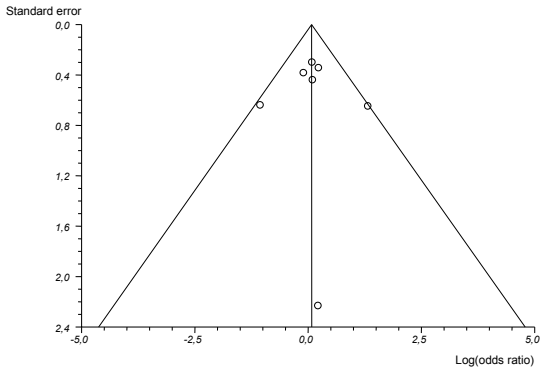


Figure 4.7.: Funnel plot showing log(OR)s and standard errors for the association of IL10 -1082 GG genotype with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.9591.

4.2.3. PTPN22 variant rs2476601 (R620W)

The PTPN22 gene on 1p13 seems to play an important role in the genetic susceptibility to autoimmune diseases in general (see section 4.1.2). Initially, it was associated with diabetes mellitus type 1 [45] and then it was tested in similar traits like Grave's disease, systemic lupus erythematosus, rheumatoid arthritis as well as psoriasis and psoriatic arthritis [276].

It encodes the lymphoid-specific phosphatase which inhibits T-cell activation and thus modulates immune response. Subsequent association studies showed positive reports for SNPs rs1217414, rs3789604 and rs2476601 (R620W) (Table B.1, p. 235). Yet only the latter was investigated sufficiently frequent to perform a meta-analysis.

Studies excluded from the meta-analysis. A family study was published by Nistor et al 2005 [338]. They were not able to achieve significant evidence for an association in 517 Caucasian families. Yet their calculations showed sufficient power to detect association by the transmission/disequilibrium test except for a recessive model. They conceded that their negative result could be due to a lack of association, the occurrence of a recessive model or a weak effect.

Studies included in meta-analysis. For the meta-analysis six case-control studies comprising eight independent cohorts with 2701 cases and 4685 controls were identified. They all met the inclusion criteria and were classified according to the clinical subtype of psoriasis investigated. Table 4.5 provides the leading author, year of publication, country and ethnicity, clinical variant of psoriasis, numbers and variant allele frequencies of patients and controls, mean age at onset (with standard deviation or range) and percentage of male patients for all cohorts.

The involved studies show some similarities and some differences. For instance, all studies were carried out in European countries like the United Kingdom, Germany or Greece as well as countries where subjects were of European descent like the United States or Canada. No investigations on other ethnicities have been identified. The percentage of male patients ranged from 32.0% to 61.0%.

According to clinical subtype of psoriasis, there were two cohorts consisting of psoriasis vulgaris patients, three cohorts of psoriatic arthritis patients and three cohorts did not specify the clinical subtype. Both psoriasis vulgaris cohorts consisted mainly of patients with an early-onset form (<40 years) of the disease. Hinks et al 2005 [182] comprised exclusively such patients and Huffmeier et al 2006 [204] mostly (concrete percentage not available). Another study by Smith et al 2008 [438] comprised exclusively early-onset psoriasis patients as well. The remaining studies did not state a distribution of onset types, mean ages at onset varied between 20 years and 29.3 years.

Results of the meta-analysis. The results of the performed meta-analysis for the PTPN22 rs2476601 (R620W) polymorphism are summarized in Figure 4.8. The genetic variant in question did not show a significant association (OR = 1.08, 95% CI = 0.94-1.23, P = 0.2714). Though individual association estimates varied between 0.39 and

Table 4.5.: Characteristics of studies included in meta-analysis of PTPN22 rs2476601 (R620W) polymorphism in psoriasis

			Numbers		Frequency			
Study [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**Onset**	**Male**
Zervou 2010 [554]	Greece (E)	P	173	348	-	-	-	-
Smith 2008 [438]	UK (E)	P1	505	393	10.0	9.2	20.0	53.8
Criswell 2005 [107]	US (E)	P	51	2064	7.8	8.5	-	32.0
Huffmeier 2006 [204]	Germany (E)	PV (most P1)	793	937	11.3	9.7	21.6 (9.8)	59.0
Hinks 2005 [182] $^{\Phi}$	UK (E)	PV1	279	595	9.1	10.3	≤ 40	-
Butt-1 2006 [56]	Canada (E)	PA	238	149	10.5	10.4	29.3 (14.2)	53.0
Butt-2 2006 [56]	Canada (E)	PA	207	199	13.8	8.5	26.8 (12.1)	61.0
Hinks 2005 [182] $^{\Phi}$	UK (E)	PA	455	595	9.9	10.3	-	-
Total			2701	4685	10.3	9.4		

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Frequency, frequency of the PTPN22 R620W T allele in %; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Onset, mean age at onset with standard deviation or range in brackets; Male, percentage of male patients in %; P, psoriasis without further specification; PV, psoriasis vulgaris; PV1, early-onset psoriasis vulgaris (Type 1); PA, psoriatic arthritis; $^{\Phi}$, these two studies use the same control subjects; - , data not provided in the article;

1.75, no significant heterogeneity among the studies was detected by Cochran Q test (P = 0.194). Thus a fixed effects model was used for the combined analysis. Funnel plot analysis provided a symmetrical shape (Figure 4.9) and Egger's regression test did not detect publication bias either (P = 0.4119).

Only one out of eight cohorts had achieved statistical significance for the association of PTPN22 R620W polymorphism and psoriasis. This cohort involved psoriatic arthritis cases, indicating a possible phenotype-dependent association. Yet two further psoriatic arthritis did not reach significance and an overall analysis of this three cohorts failed to affirm an association (OR = 1.10, 95%CI = 0.88-1.38, P = 0.3865). A combined analysis of psoriasis phenotypes without joint involvement remained insignificant as well (OR = 1.06, 95%CI = 0.90-1.25, P = 0.464).

Studies involving exclusively or mainly early-onset psoriasis did not stick out from the analysis, not indicating an onset-dependent mode of inheritance. Yet most studies showed a rather low mean age at onset. Regarding ethnicity, no stratification was feasible as all cohorts had a European background. Allele frequencies were very similar in all control populations as well, ranging from 8.5% to 10.4%. Gender did not seem to have an influence on association estimates either.

Discussion of the meta-analysis. The present meta-analysis on the association between PTPN22 rs2476601 (R620W) polymorphism and psoriasis did not yield significant evidence. This is not surprising as only Butt et al 2006 [56] had reported a modest association for one of their psoriatic arthritis cohorts (Butt-2). Further case-control studies

and a family study by Nistor et al 2005 [338] did not replicate this finding.

A false-positive association by Butt et al 2006 [56] might be due to population stratification in their cohort, especially since there had been larger studies with contradictory results in the first place. A phenotype (psoriatic arthritis) and population (Toronto) specific association remains at least conceivable though. [56]

Yet two further psoriatic arthritis cohorts did not replicate the association, thus standing against the hypothesis of a phenotype dependent association. Regarding ethnicity, no statement on the inheritance in non-Caucasian populations can be made as all subjects included in the meta-analysis were from European descent. Genetic predispositions might differ across ethnicities. In addition, there were no hints for a dependency on onset type or gender.

In conclusion, the meta-analysis indicates a lack of association for PTPN22 rs2476601 (R620W) polymorphism with psoriasis, which is in conformity with the result of the excluded study by Nistor et al 2005 [338]. Yet another SNP, rs3789604, was replicated in two large case-control studies on Caucasian populations [283, 438], supporting PTPN22 as a candidate gene.

Relating to functional relevance, the phosphatase encoded by PTPN22 plays an important role in T cell inhibition. The amino acid exchange from arginine to tryptophan (R602W) leads to a disruption of the said inhibition. The T cell hyperresponsiveness caused thereby in turn promotes autoimmunity. This hypothesis was supported by *in vitro* and *knock-out* experiments. [45, 45, 170]

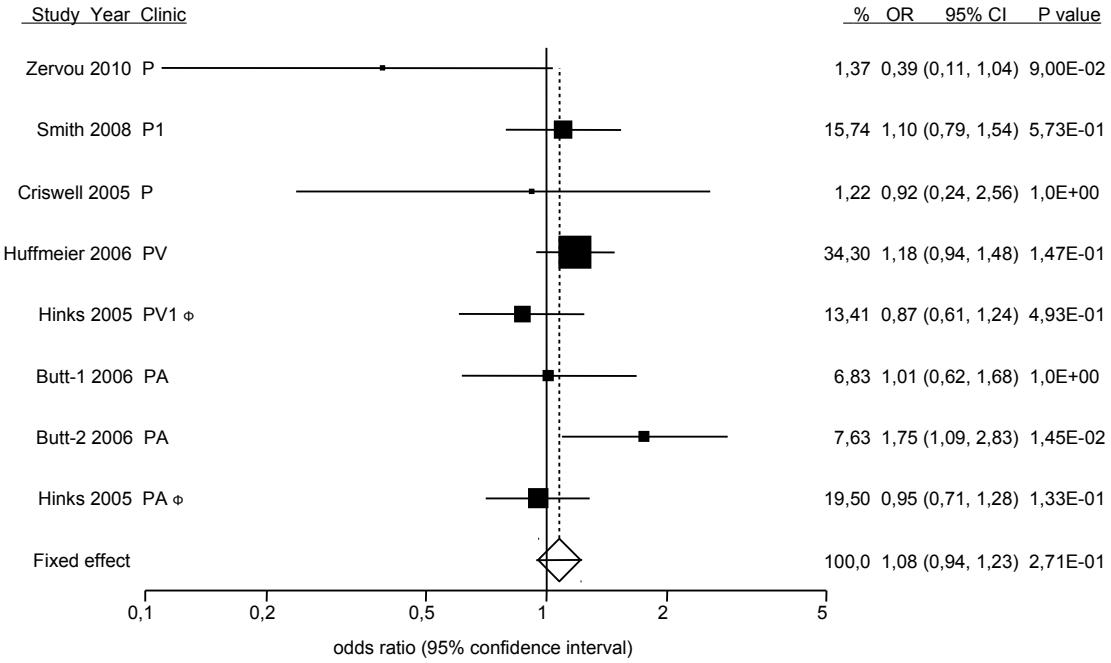


Figure 4.8.: Association of PTPN22 rs2476601 T allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.5.

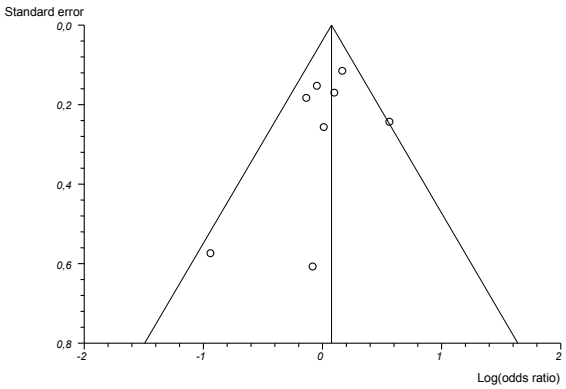


Figure 4.9.: Funnel plot showing the log(OR)s and standard errors for the association of PTPN22 rs2476601 T allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.4119.

4.2.4. VDR variants ApaI, TaqI and BsmI

The local application of vitamin D analogs has long been used as a treatment for psoriasis. Consequently, genetic variants in the vitamin D receptor (VDR) gene were suspected to be markers of responsiveness or could play a role in psoriasis pathogenesis (see section 4.1.2). Kontula et al 1997 [252] did not find significant differences in allele frequencies between responders and non-responders in their small sample set, but polymorphisms showed association with psoriasis in other cohorts.

To date four restriction fragment length polymorphisms (FokI, ApaI, TaqI and BsmI) and the A-1012G promoter polymorphism were tested for association with psoriasis. While the promoter polymorphism and FokI showed only negative reports (Table B.2, p. 243), the remaining restriction fragment length polymorphisms had been associated in sufficient case-control studies to perform meta-analyses.

Studies excluded from the meta-analyses of ApaI, TaqI and BsmI. Kontula et al 1997 [252] studied the relation between VDR BsmI polymorphism and responsiveness to calcipotriol treatment in Finnish psoriasis patients. The genotyping of 10 responders and 9 non-responders, however, showed similar b allele frequencies in both groups. The overall frequencies of the b allele in the 19 psoriasis patients (58%) did not differ significantly from those in healthy blood donors (67%) of another study (Viitanen et al 1996 [507]). As there were only 19 affected and 75 unaffected subjects, the sample size was too small to take the study into account for the meta-analysis.

Studies included in the meta-analyses of ApaI, TaqI and BsmI. Finally, seven studies met the inclusion criteria for ApaI and six studies for TaqI and BsmI. For all studies some characteristics like leading author, year of publication, country and ethnicity, clinical variant of psoriasis, numbers and variant allele frequencies of patients and controls and percentage of male patients are listed in Table 4.6.

Studies were performed on subjects suffering from different clinical subtypes of psoriasis. There were five studies on psoriasis vulgaris samples and three on mixed samples including psoriatic arthritis, guttate psoriasis or palmoplantar pustulosis. The remaining studies did not comment on psoriasis subtype.

In addition, the studies involved both subjects with early-onset psoriasis and with late-onset psoriasis. Whenever provided, the percentage of early-onset psoriasis patients tended to be high. The studies by Halsall et al 2005 [164] and Park et al 1999 [366] carried out a direct comparison between onset types.

Regarding ethnicity, most studies were carried out in Asia or Europe. There were four cohorts from Asian populations, five from European populations and one from Egypt. The age range of participants stretched form childhood or adolescence to old age. Yet no data was provided in Mee et al 1998 [310] and no range was provided in Saeki et al 2002 [408]. Similarly, the percentage of male patients varied from 43.1% to 76.7% between studies. Sample sizes of all studies were rather small.

Table 4.6.: Characteristics of studies included in meta-analyses of VDR polymorphisms in psoriasis

					Frequencies						
			Numbers		ApaI		TaqI		BsmI		
Study [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**Male**
Park 1999 [366] $^{\Phi}$	Korea (A)	P (83%)	104	104	68.3	83.2	-	-	-	-	50.0
Mee 1998 [310]	UK (E)	P	175	124	-	-	-	-	58.0	54.0	-
Zuel-Fakkar 2010 [564]	Egypt	PV (62%)	50	50	70.0	66.0	57.0	64.0	-	-	62.0
Halsall 2005 [164]	DK (E)	PV (85%)	205	80	-	-	64.0	56.0	-	-	58.0
Ruggerio 2004 [405]	Italy (E)	PV (63%)	60	68	-	-	-	-	51.7	49.9	76.7
Saeki 2002 [408]	Japan (A)	PV	115	69	72.2	66.7	93.0	85.5	91.3	81.2	64.3
Lee 2002 [270] $^{\Phi}$	Korea (A)	PV	55	104	65.5	83.2	-	-	95.5	93.6	52.7
Dayangac-E 2007 [108]	Turkey (E)	PVA (96%)	51	100	52.0	57.5	73.5	59.5	-	-	43.1
Kaya 2002 [237]	Turkey (E)	PVG	53	54	55.7	69.4	59.4	63.0	57.5	59.3	-
Okita 2002 [353]	Japan (A)	PVP (49%) $^{\#}$	50	86	73.0	65.7	89.0	91.9	87.0	88.4	70.0
Total ApaI			478	463	42.7	46.2					
Total TaqI			524	439			72.7	70.0			
Total BsmI			508	505					72.9	71.1	

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Frequencies, frequencies of ApaI, TaqI and BsmI in %; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Male, percentage of male patients in %; DK, Denmark; P, psoriasis without further specification; PV, psoriasis vulgaris; PA, psoriatic arthritis; PVA, psoriasis vulgaris and psoriatic arthritis; PVG, psoriasis vulgaris and guttate psoriasis; PVP, psoriasis vulgaris and palmoplantar pustulosis; $^{\Phi}$, these two studies use the same control subjects; $^{\#}$, 38 with psoriasis vulgaris, 10 with palmoplantar pustulosis or psoriasis pustulosa, 1 with psoriatic arthritis and 1 with acrodermatitis continua; - , data not provided in the article;

Results of the meta-analysis of ApaI. Of the seven studies, two showed a significant association between the VDR ApaI A allele and psoriasis. These involve the first description by Park et al 1999 [366] and a cohort of Lee et al 2002 [270]. Interestingly, both studies used the same control population and were the only ones carried out in Korea. Another study by Kaya el al 2002 [237] reached borderline significance in a Turkish population. The remaining studies, however, were not able to confirm a risk conceded by the ApaI variant.

The overall meta-analysis lacked evidence for an association between the RFLP and psoriasis as well (OR = 1.09, 95%CI = 0.69-1.70, P = 0.7223). A random effects model was applied for the calculation as Cochran Q test revealed significant heterogeneity between the studies ($P < 0.0001$) with odds ratios ranging from 0.55 to 2.61 (Figure 4.10). No publication bias was detected using Egger's regression test (P = 0.8274) and funnel plot analysis (Figure 4.11).

As the significant results on Korean populations were not replicated by further Asian studies on Japanese populations, a ethnicity dependent pattern of inheritance seems unlikely. Still, a strictly population specific (Korea) association remains at least conceivable.

The relation between ApaI polymorphism and psoriasis found in Park et al 1999 [366]

was even stronger in early-onset subjects. Yet Dayangac-Eden et al 2007 [108] did not report an association for their mainly early-onset cohort (96%), arguing against the hypotheses of a dependency on age at onset.

Regarding phenotypes, significant outcomes were achieved in a psoriasis vulgaris sample and a unspecified sample. In addition, borderline significance was achieved in a mixed sample involving psoriasis vulgaris and guttate psoriasis. The significance increased when guttate psoriasis cases were excluded. Still, a disease specific (psoriasis vulgaris) association seems unlikely as two more studies on this subtype did not replicate the finding.

Results of the meta-analysis of TaqI. Two studies out of six showed a significant association between the VDR TaqI T allele and psoriasis. Those two studies were carried out in different countries with different ethnicities and involved different psoriasis subtypes. In addition, the male/female ratio was high in the one study while it was low in the other. This makes a population, phenotype or gender specific association unlikely. The remaining studies, however, did not achieve significant association estimates.

The present meta-analysis did not yield a significant evidence of association either (OR = 1.24, 95%CI = 0.98-1.57, P = 0.069) (Figure 4.12). Individual odds ratios ranged from 0.72 to 2.27 and Cochran Q test did not reveal significant heterogeneity between the studies (P = 0.0639). Thus a fixed effects model was applied for the calculation. No publication bias was detected using Egger's regression test (P = 0.6663) and the funnel plot shows a symmetrical shape (Figure 4.13).

Concerning phenotypes, there were significant association estimates for a psoriasis vulgaris cohort and a mixed cohort involving psoriatic arthritis. A separate investigation of phenotypes in Dayangac-Erden et al 2007 [108] showed an even stronger association for psoriatic arthritis. Similarly, a separate investigation of psoriasis vulgaris and guttate psoriasis in Kaya et al 2002 [237] showed higher estimates for guttate psoriasis. Yet data is insufficient to derive a phenotype dependent association from this.

Relating to different onset types, one of the significant studies involved of 96% early-onset subjects (Dayangac-Erden et al 2007 [108]) while the other did not state the distribution of onset types. Yet another sample consisting of 85% early-onset subjects did not reach significance. In addition, a direct comparison by Halsall et al 2005 [164] did not show differences in T allele frequencies between early-onset subjects (65%) and late-onset subjects (63%). This makes an onset-type dependent pattern of inheritance unlikely. Yet data is limited and therefore additional studies with direct comparisons would be needed to assess the matter.

The association did not seem to depend on ethnicity either as the two samples with significant associations were form Japan and Turkey. In addition, the other samples from Asia, Europe and Egypt did not reach significance. The same applies for male/female ratios, being high in one significant study and low in the other. This supports the hypothesis of a gender independent association.

Results of the meta-analysis of BsmI. Of the six publications solely Saeki et al 2002 [408] reported a significant association between the VDR BsmI b allele and psoriasis. Interestingly, this study does not display a characteristic that would explain a specific association. The study sample consists of Asian psoriasis vulgaris patients with a sightly elevated male/female ratio just like the samples of Okita et al 2002 [353] and Lee et al 2002 [270]. Still, the remaining studies were not able to replicate the finding of Saeki et al 2002 [408].

The overall meta-analysis lacks evidence for an association between the RFLP and psoriasis (OR = 1.16, 95%CI = 0.93-1.46, P = 0.1941). A fixed effects model was applied for the calculation as Cochran Q test revealed no significant heterogeneity between the studies (P = 0.2698). The forest plot in Figure 4.14 shows the individual association estimates ranging from 0.88 to 2.44 and the combined estimate. No publication bias was detected using Egger's regression test (P = 0.7735) and the funnel plot describes a symmetrical shape (Figure 4.15).

As the significant result in a Japanese psoriasis vulgaris cohort was not replicated in another study on Japanese patients, a population dependent pattern of inheritance seems unlikely. The same is true for the clinical subtype, as other studies on psoriasis vulgaris lacked evidence for association. Relating to a putative dependency on age at onset, no statement can be given as no distribution of onset types was provided in the significant study by Saeki et al 2002 [408].

Discussion of the meta-analyses of ApaI, TaqI and BsmI. The present meta-analyses did not reach statistical significance for associations between the restriction fragment length polymorphisms and psoriasis. In detail, there had been three positive reports for ApaI, two for TaqI and one for BsmI. For the latter there had been an additional negative report in a study excluded from the meta-analysis [252]. For all polymorphisms there were no clear indications for dependency on characteristics like clinical psoriasis subtype, onset type, gender or ethnicity.

Yet for TaqI, a direct comparison of different clinical variants showed a slightly higher degree of association for psoriatic arthritis than for psoriasis vulgaris (Dayangac-Erden et al 2007 [108]). The association estimates for guttate psoriasis were more pronounced for TaqI and less pronounced for ApaI (Kaya et al 2002 [237]). Concerning onset types, a direct comparison for ApaI showed a stronger association with early-onset psoriasis (Park et al 1999 [366]). Yet none of these findings were replicated.

In spite of lacking evidence for association with psoriasis in meta-analyses, vitamin D has both functional and therapeutic relevance in autoimmune diseases in general. It plays a role in the innate as well as the acquired immune system and experimental animal models have shown that vitamin D supplementation is able to prevent the development of autoimmune diseases. In addition, vitamin D receptor polymorphisms have been associated with traits like inflammatory bowel disease, Grave's disease or rheumatoid arthritis. [257]

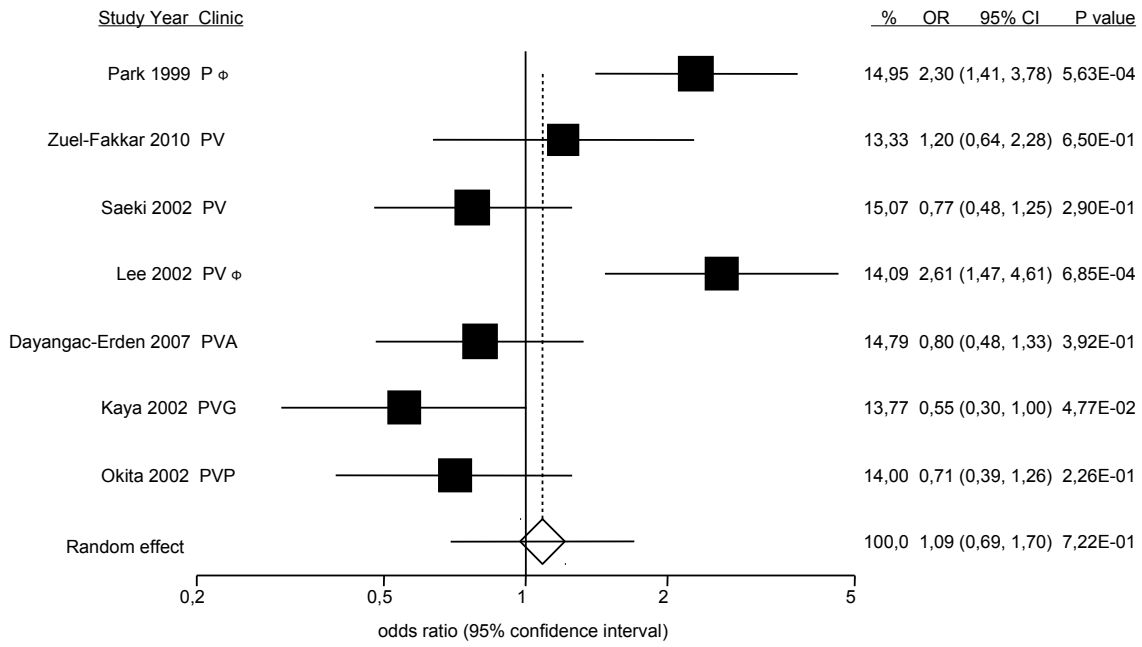


Figure 4.10.: Association of VDR ApaI A allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.6.

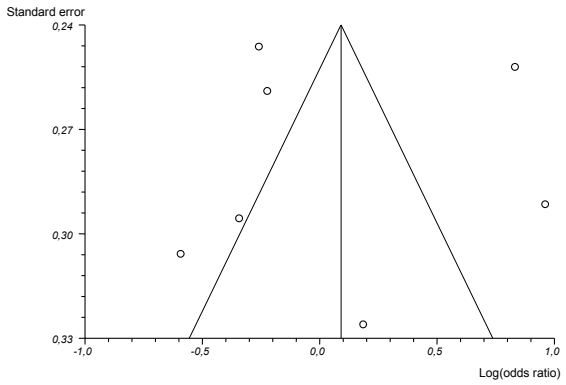


Figure 4.11.: Funnel plot showing log(OR)s and standard errors for the association of VDR ApaI A allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.8274.

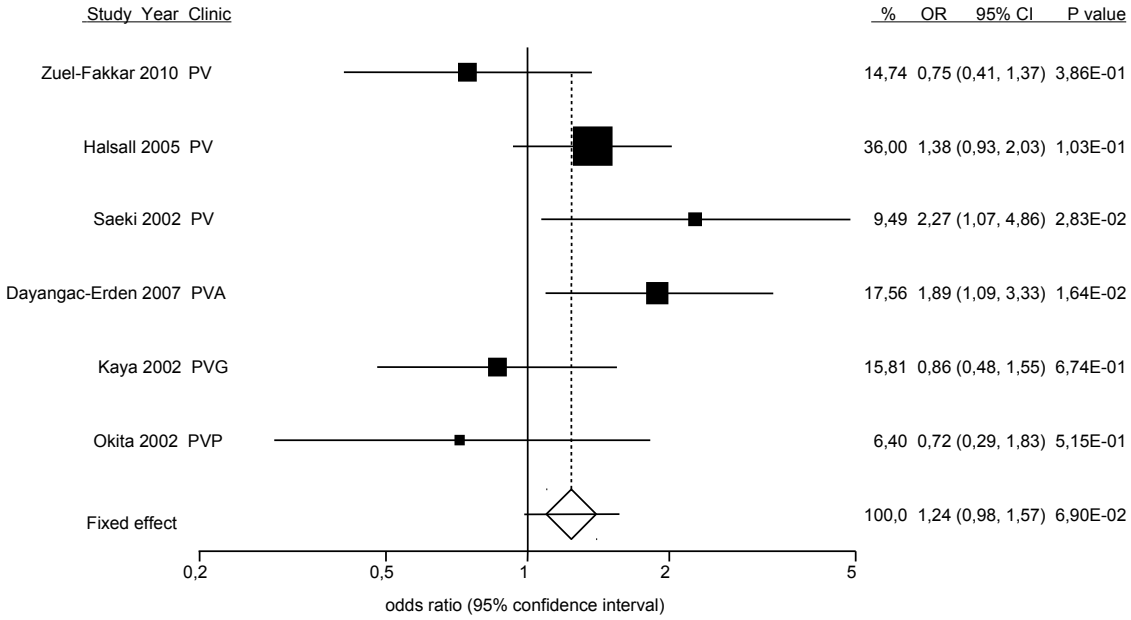


Figure 4.12.: Association of VDR TaqI T allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.6.

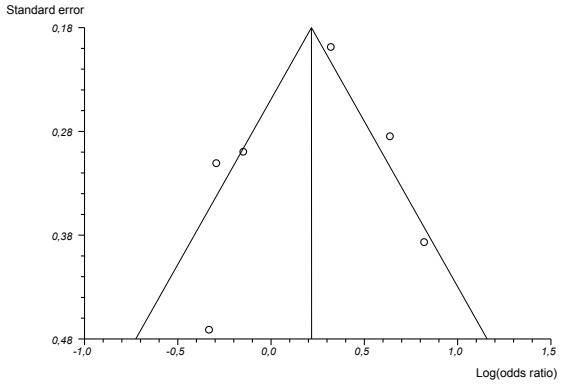


Figure 4.13.: Funnel plot showing log(OR)s and standard errors for the association of VDR TaqI T allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.6663.

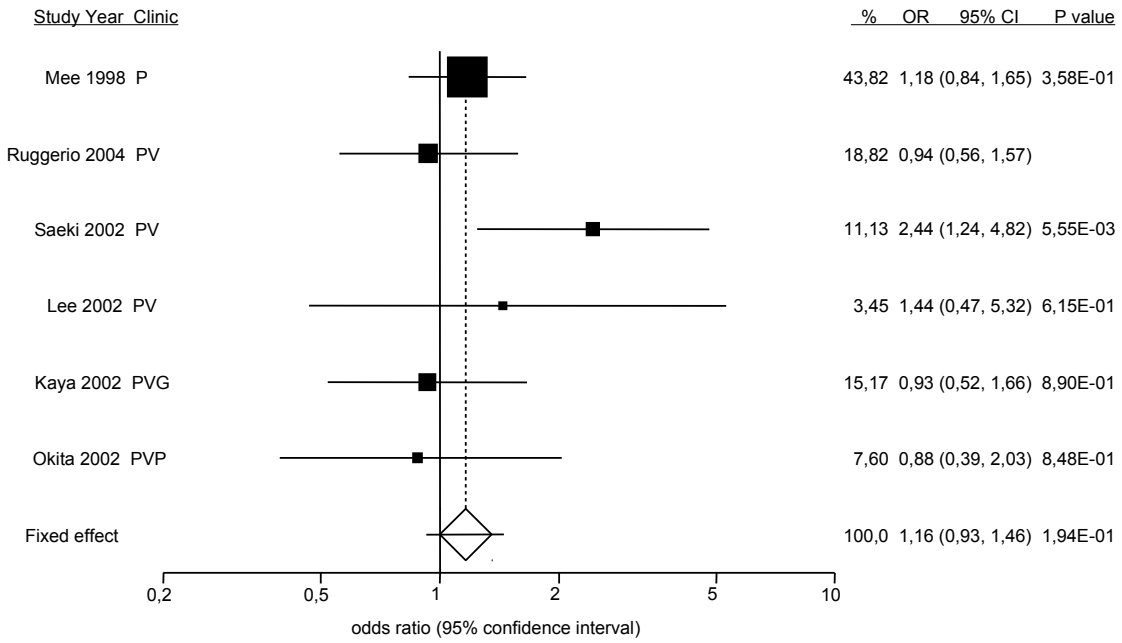


Figure 4.14.: Association of VDR BsmI b allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.6.

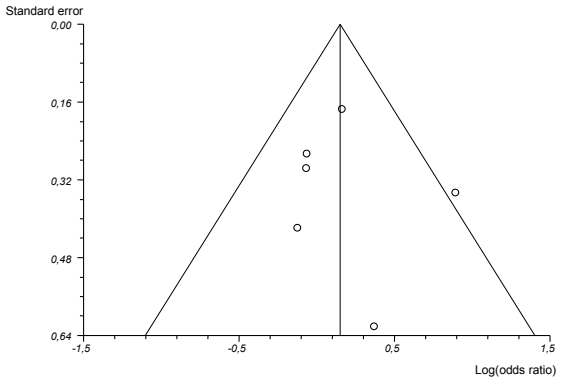


Figure 4.15.: Funnel plot showing log(OR)s and standard errors for the association of VDR BsmI b allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.7735.

4.2.5. ACE insertion/deletion

Angiotensin converting enzyme (ACE) is expressed in many different tissues like for example the skin and immune cells. Its biological effect is said to be proinflammatory and an essential role in functional activities of the skin is suspected [103]. Finally, the potential induction and exacerbation of psoriatic lesions by treatment with ACE inhibitors promoted ACE as a candidate gene for psoriasis (see section 4.1.2).

The first study trying to find out if genetic variants in the ACE gene increased the susceptibility to psoriasis was carried out by Ozkur et al 2004 [363]. Since then, the 287-base pair insertion/deletion (I/D) polymorphism in intron 16 [515] was investigated by seven association studies.

Studies included in the meta-analysis. As all studies met the inclusion criteria, seven independent cohorts with 1065 cases and 1547 controls could be included in the meta-analysis. Table 4.7 presents some characteristics of the studies like leading author, year of publication, country, clinical variant of psoriasis, numbers and variant allele frequencies of patients and controls and percentage of male patients for all cohorts. Whenever available numbers of early-onset and late-onset subjects and corresponding allele frequencies were listed.

Concerning different psoriasis phenotypes, there were three cohorts consisting of common psoriasis vulgaris cases as well as two cohorts consisting of psoriatic arthritis cases. The remaining cohorts were not characterized concerning clinical subtype. Interestingly, Shehab et al 2008 [430] studied additional phenotypes of spondylarthropathies apart from psoriatic arthritis including ankylosing spondylitis.

Nearly all publications provided data on different onset-types. Most of the times a higher number of early-onset subjects was involved (Table 4.7). Shehab et al 2008 [430], however, stated the distribution of patients with onset before and after 40 years for all subjects suffering from different kinds of spondylarthropathies and not for psoriatic arthritis in particular.

Regarding ancestry, only one study had been carried out on an Asian population from Taiwan while four studies involved participants from European countries like Spain, Greece, Austria and Turkey. Two more studies investigated Arab subjects from Kuwait which are the result of an admixture with other populations and include many immigrants [430]. The percentage of male patients varied from 75.3% to 37.3% between studies (Table 4.7). Again Shehab et al 2008 [430] provided this information only for the whole study population suffering from different spondylarthropathies.

Results of the meta-analysis. The results of the meta-analysis for the homozygous ACE insertion genotype are summarized in Figure 4.16. Odds ratios ranged from 0.48 to 1.76, but as Cochran Q test did not reveal a significant deviation from the homogeneity assumption (P = 0.1217) a fixed effects model was applied. The outcome indicates an association between the homozygous ACE insertion and psoriasis (OR = 1.25, 95%CI = 1.02-1.52, P = 0.0293). The funnel plot analysis conducted to detect publica-

Table 4.7.: Characteristics of studies included in meta-analysis of ACE ins/del polymorphism in psoriasis

			Numbers				Frequencies				
Study [Ref]	**Country**	**Clinic***	**P**	**P1**	**P2**	**C**	**P**	**P1**	**P2**	**C**	**Male**
Chang 2007 [75]	Taiwan	P (61%)	312	191	121	615	72.4	71.5	74.0	68.2	75.3
Veletza 2008 [506]	Greece	PV (63%)	128	81	47	113	31.6	34.6	26.6	32.3	60.2
Weger 2007 [515]	Austria	PV (66%)	207	136	71	182	51.7	53.3	48.6	55.2	71.0
Ozkur 2004 [363]	Turkey	PV (71%) #1	86	61	25	154	37.2.8	40.2	28.0	40.6	51.2
Shehab 2008 [430]	Kuwait	PA	13	-	-	111	23.1	-	-	25.3	-
Al-Awadhi 2007 [2]	Kuwait	PA (53%)	51	27	24	100	32.4	25.9	39.6	36.5	37.3
Coto-Segura 2009 [103]	Spain	PPA (71%) #2	268	191	77	272	37.3	37.4	37.0	39.2	53.0
Total			1065	687	365	1547	40.8	43.8	42.7	42.5	58.0

Study, given by first author and year of publication; Ref, reference; Country, country where the study was carried out; Numbers, numbers of patients and controls; P, patients; C, controls; P, psoriasis; P1, early-onset psoriasis (Type 1); P2, late-onset psoriasis (Type 2); Frequency, frequency of the ACE insertion in %; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Male, percentage of male patients in %; P, psoriasis without further specification; PV, psoriasis vulgaris; PA, psoriatic arthritis; PPA, psoriasis without further specification and psoriatic arthritis; #1, 3.5% palmoplantar pustulosis, 2.3% psoriatic erythroderma; #2, 20.5% psoriatic arthritis; - , data not provided in the article;

tion bias provides a symmetrical shape (Figure 4.17) and Egger's regression test did not detect any significant publication bias either (P = 0.1467).

Stratification by clinical variants or ethnicity did not result in any substantial changes, thus not indicating different patterns of inheritance. Two additional meta-analyses on early-onset subjects and late-onset subjects separately, however, indicated a slight dependence on age at onset. Patients with late-onset psoriasis tended to show a slightly stronger but still insignificant association to the homozygous ACE insertion genotype.

- Early-onset: OR = 1.01, 95%CI = 0.64-1.59, P = 9.63E-01 Fig. 4.18a, 4.19a
- Late-onset: OR = 1.27, 95%CI = 0.94-1.71, P = 1.20E-01 Fig. 4.18b, 4.19b

Discussion of the meta-analysis. The present meta-analysis supported an association of the homozygous ACE insertion genotype with psoriasis. Two of seven case-control studies had found a significant correlation. Neither stratification by ethnicity nor by clinical variant promoted associations with particular subsets. Only a slight dependency on the age at onset was observed, favoring an association with late-onset psoriasis.

Interestingly, Shehab et al 2008 [430] supported an additional association to another inflammatory spondylarthropathy, ankylosing spondylitis. This might account for a role of the ACE polymorphism in inflammatory processes in general. This hypothesis was supported by the finding that the ACE activity was higher in inflammatory arthritis than in non-inflammatory arthritis [505]. In addition to that, an expression analysis showed that the ACE I allele was related to lower plasma and tissue levels of angiotensin converting enzyme [397].

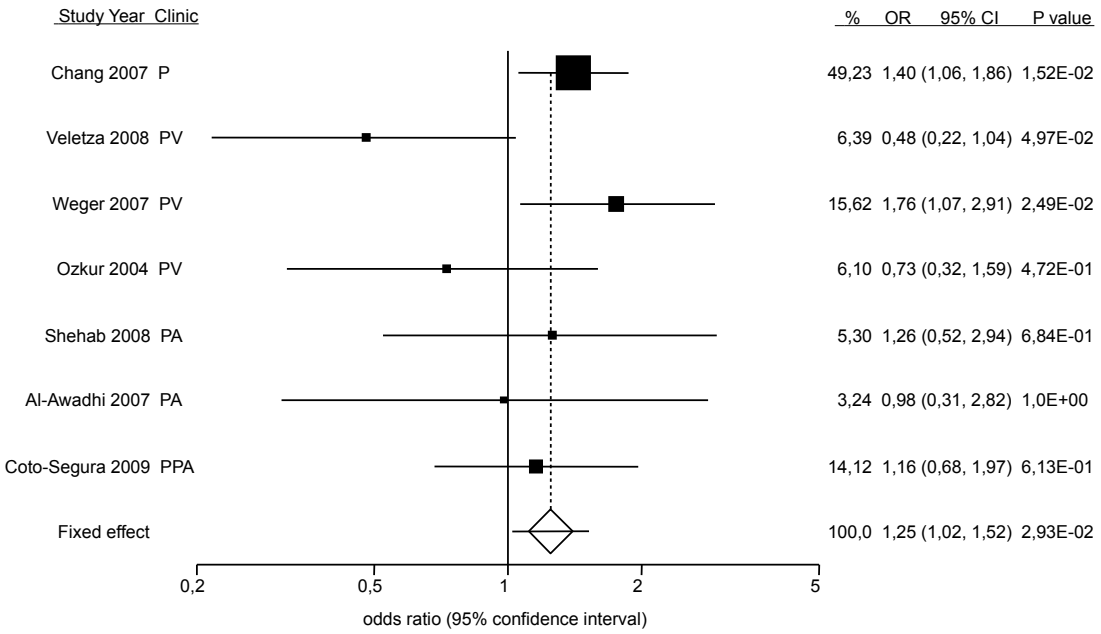


Figure 4.16.: Association of homozygous ACE insertion with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.7.

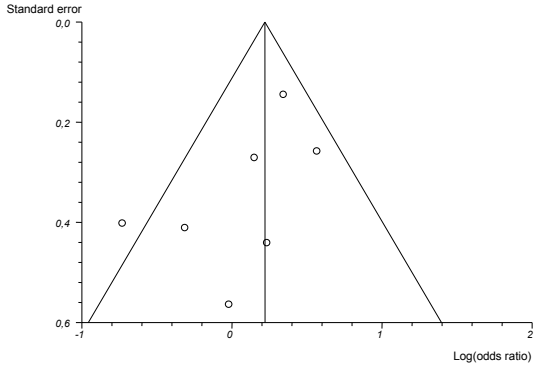
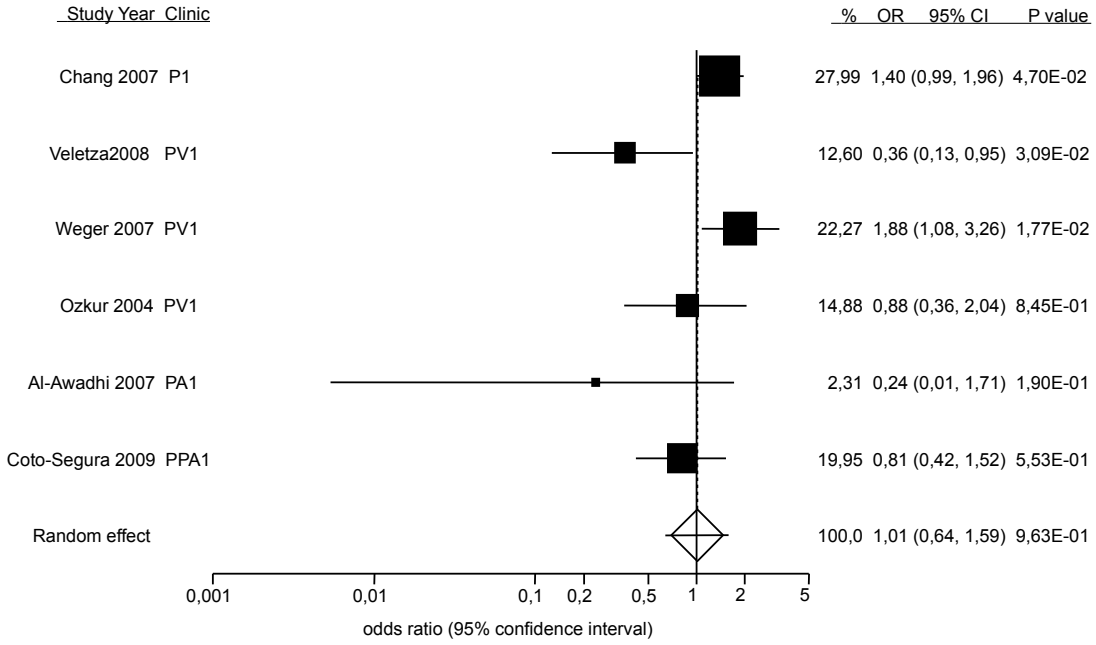
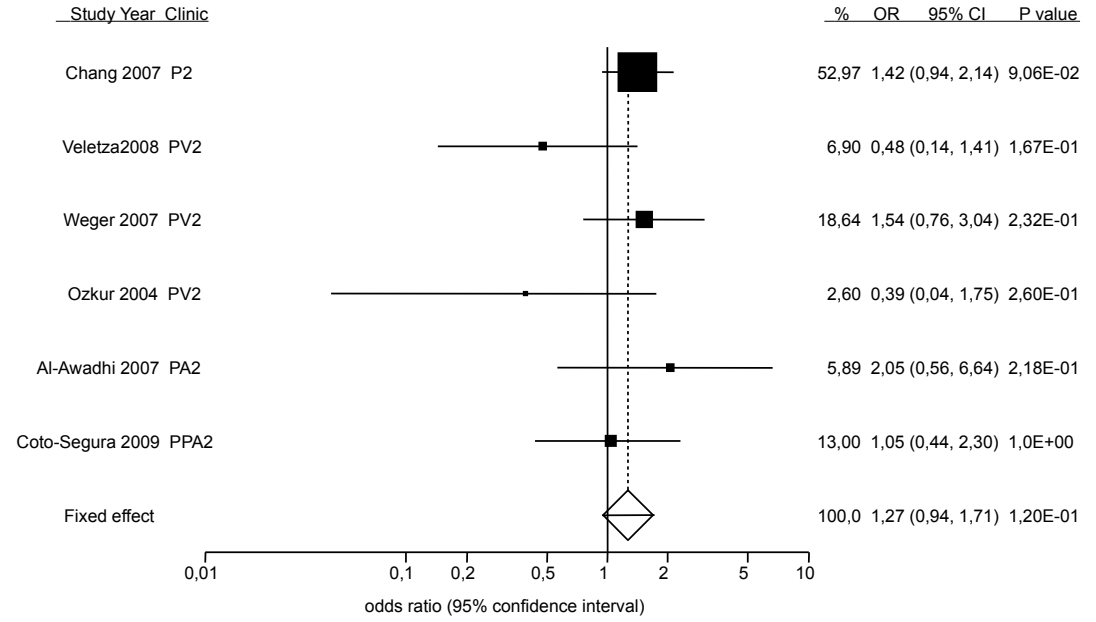


Figure 4.17.: Funnel plot showing log(OR)s and standard errors for the association of homozygous ACE insertion with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.1467.

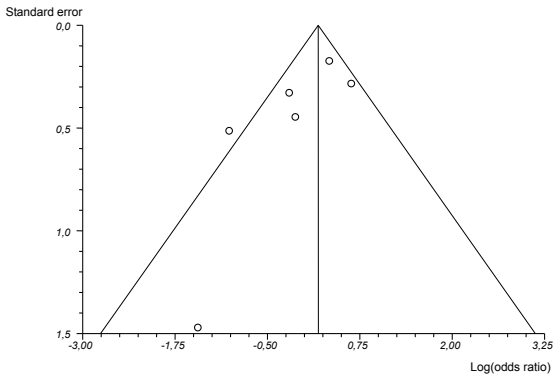


(a) Early-onset

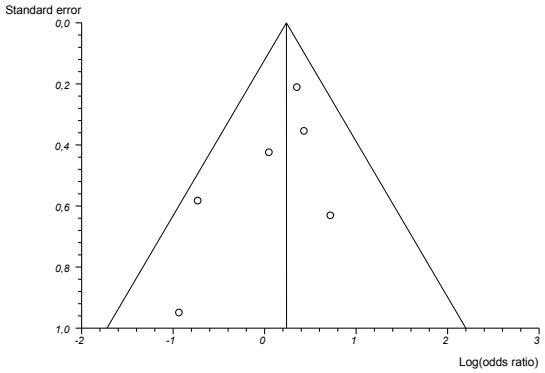


(b) Late-onset

Figure 4.18.: Association of homozygous ACE insertion with (a) early-onset and (b) late-onset psoriasis. Forest plots showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analyses. Abbreviations see Table 4.7.



(a) Early-onset



(b) Late-onset

Figure 4.19.: Funnel plots showing log(OR)s and standard errors for the association of ACE insertion with (a) early-onset and (b) late-onset psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P values > 0.05; (a) $P = 0.109$; (b) $P = 0.2236$.

4.2.6. VEGFA variant +405G

The VEGFA gene is located on chromosome 6p21.1 near the PSORS1 risk locus. It encodes the vascular endothelial growth factor type A which seems to play a role in the inflammatory course of psoriasis (see section 4.1.2). Hereby, an over-expression of VEGFA in endothelial cells causes an excessive angiogenesis probably leading to an increased leakiness of the microvasculature which in turn promotes the migration of leukocytes into the inflamed skin. As a consequence, genetic variants in the VEGFA gene are putative candidates for the susceptibility to psoriasis.

Positive associations with various different variants including +405G, -460C, +936T and -152G/A have been reported (Table B.1, p. 235). A strict replication in independent sample sets, however, was only achieved for two of them. For -460C there were four case-control studies, two reporting a positive result and two reporting a negative results.

Findings of an existing meta-analysis. For +405G a meta-analysis involving seven cohorts was performed by Wu et al 2010 [537]. Three cohorts were from European [55, 29, 547] and four from Asian ancestry [537, 534, 273, 512] including a northern Chinese Han population investigated by Wu et al themselves.

They found that the VEGFA variant +405G was associated with psoriasis (OR = 1.17, 95%CI = 1.05-1.31, P = 0.04), especially in patients from Asian ancestry (OR = 1.28, 95%CI = 1.12-1.47, P = 0.0003). For the group of European studies, on the contrary, a similar association with the disease could not be confirmed (OR = 0.96, 95%CI = 0.79-1.17, P = 0.70). From their point of view, this might be due to either geographically different patterns of inheritance or inconsistency between studies.

Interestingly, a study by Young et al 2004 [547] stuck out from the meta-analysis. Their sample of exclusively early-onset subjects produced a very low odds ratio of 0.68 compared to the other odds ratios ranging from 1.06 to 1.38. In addition, it is noteworthy that Butt et al 2007 [55] included subjects with co-existing joint involvement which might cause bias. In conclusion, the authors state that further case-control data on the association between European populations and the VEGFA +405 G allele would be necessary in the future.

Discussion of the existing meta-analysis. As no additional association studies have been carried out since the publication of the meta-analysis, the association between European populations and the VEGFA +405 G allele remains unclear while there was a positive result for Asian populations.

Relating to functional relevance, however, there was a review article by Canavese et al 2010 [61]. They supported the pro-inflammatory role of vascular endothelial growth factor in the pathogenesis of psoriasis and its role as a target for novel therapies. For example, anti-VEGF treatment showed effectiveness in mouse models and in patients with psoriasis who received the anti-VEGF therapy for cancer. Thus, this study validates VEGFA as a candidate gene for psoriasis in addition to the positive result of the meta-analysis.

4.2.7. LCE variants LCE3C_LCE3B deletion and rs4112788

The LCE gene cluster is located within the epidermal differentiation complex (EDC) on chromosome 1q21 which is also one of the psoriasis susceptibility loci identified by genetic linkage analyses (PSORS4). The LCE genes encode for late cornified envelope proteins. Together with involucrin, loricrin and especially filaggrin they are indispensable for the development and the function of the epidermis. As hyperproliferation and dysfunction of the epidermis form part of the pathogenesis, mutations in LCE genes are candidates for psoriasis susceptibility (see section 4.1.2).

Consequently, a considerable number of studies were performed on the association of different LCE genes and psoriasis. There were positive reports for polymorphisms in LCE1A, LCE1C, LCE2A, LCE3A, LCE3B and LCE3C (Table B.1, p. 235). For some of them there has been no attempt to replicate the finding and for others replication was searched but failed. For LCE3A variants rs4845454 and rs1886734, however, replication was successful in three independent cohorts [557].

Findings of an existing meta-analysis. For the deletion of LCE3C/B and the tag SNP rs4112788 there was even more supporting evidence. First, de Cid et al 2009 [98] performed a comprehensive multi-center analysis including four individual cohorts from European ancestry. The samples from Spain, the Netherlands, Italy and the United States were investigated individually and together. All of these association analyses reached a significant P value with odds ratios ranging from 1.30 to 1.50. The overall estimates for all 2831 samples were as follows:

- LCE3C_LCE3B deletion: OR = 1.38, 95%CI = 1.19-1.61, P = 1.38E-08
- SNP rs4112788 C allele: OR = 1.41, 95%CI = 1.25-1.58, P = 6.56E-09

An evaluation of linkage disequilibrium (LD) between the LCE3C_LCE3B deletion and tag SNPs in the adjacent region spanning 130 kb showed that rs4112788 located 584 nucleotides downstream of LCE3D and 4.5 kb centromeric of LCE3C_LCE3B deletion was in strongest LD suggesting a single origin in populations of European ancestry. In addition, de Cid et al 2009 [98] replicated their findings in a family sample from the United States including 1395 affected in 562 families.

In order to continue their investigations on the putative association of LCE3C_LCE3B deletion and its tag SNP rs4112788 with psoriasis, the same study group performed a meta-analysis on independent case-control data. Riveira-Munoz et al 2010 [399] included 13 cohorts with a total of 9389 patients and 9477 controls from twelve different populations. Both the LCE3C_LCE3B deletion and the tag SNP rs4112788 were associated with psoriasis in all ten cohorts from European ancestry. The association estimates for the overall meta-analysis on sample sets from Finland, France, Italy, Spain, the Netherlands, Germany, the United Kingdom, Ireland and the United States were reported as follows:

- LCE3C_LCE3B deletion: OR = 1.21, 95%CI = 1.15-1.27, P = 4.58E-13
- SNP rs4112788 C allele: OR = 1.21, 95%CI = 1.15-1.27, P = 1.42E-12

The high coefficients of determination measures in all cohorts suggest that the tag SNP rs4112788 is a close proxy to the LCE3C_LCE3B deletion and therefore reaches an equally high estimate. In addition to the significant association with European cohorts, both the LCE3C_LCE3B deletion and rs4112788 showed an equally strong relation with a single cohort from China. Further studies on other Asian cohorts from Japan and Mongolia for the LCE3C_LCE3B deletion only, showed significant association estimates as well.

Findings of additional studies. During the publication process of the meta-analysis, further studies reported similar findings. For example, the first large genome-wide association study in a Chinese population by Zhang et al 2009 [557] identified a susceptibility locus in the LCE cluster as well. They found multiple significantly associated SNPs located within the same linkage disequilibrium block including rs4112788 (P = 7.13E-27) and rs4085613 (P = 6.69E-30).

Shortly thereafter, Huffmeier et al 2010 [199] performed a case-control analysis on a German cohort including 1354 cases and 937 controls. They investigated three single nucleotide polymorphisms in the LCE locus: rs10888502, rs4845456 and rs4112788. The latter polymorphism showed the strongest association with psoriasis in this sample set (OR = 1.22, 95%CI = 1.07-1.39, P = 0.002). The allele frequency of the LCE3C_LCE3B deletion was estimated to 70.9% in patients and to 64.9% in controls. Consequently, the allele frequency differed significantly between the two groups providing strong evidence for association of psoriasis with the LCE3C_LCE3B deletion (OR = 1.31, 95%CI = 1.15-1.48, P = 2.97E-05). A separate analysis of early- and late-onset psoriasis did not indicate an influence of age at onset.

In order to investigate whether the LCE gene locus was associated with psoriatic arthritis as well, Huffmeier et al 2010 [200] genotyped 650 independent German patients with additional joint involvement and 937 controls. Neither for the single nucleotide polymorphisms (rs10888502, rs4845456 and rs4112788) nor for the LCE3C_LCE3B deletion there was a significant difference in allele frequencies, thus not indicating an association.

Coto et al 2010 [102] genotyped 405 Spanish psoriasis patients and 400 healthy controls for the LCE3C_LCE3B deletion and rs4112788. The frequency of the LCE3C_LCE3B del/del genotype was significantly higher in psoriasis patients without joint involvement (n = 274) compared to controls (OR = 1.40, 95%CI = 1.03-1.92, P = 0.03), but not in the whole study sample. This shows once again that psoriatic arthritis does not seem to be associated with the LCE gene cluster. However, the analysis of the tag SNP rs4112788 did not reach statistical significance, neither for subgroups nor for the complete study sample.

Bowes et al 2010 [48] started another attempt in a further case-control study involving 1057 psoriatic arthritis patients and 5575 matched controls from the United Kingdom

and Ireland. In contrast to Huffmeier el al, they found a significant association for rs4112788 (P = 0.001) and rs4085613, another single nucleotide polymorphism mapping to the LCE gene cluster (P = 0.001). An association of the latter with skin-type psoriasis had already been found in the genome-wide association scan by Zhang et al 2009 [557].

Strange et al 2010 [453] showed evidence for association of the LCE gene locus with psoriasis in a large genome-wide association study including 2622 affected individuals and 5667 healthy controls from a UK/Irish population. The tag SNP rs4112788 located 584 nucleotides downstream of LCE3D and 4.5kb centromeric of LCE3C_LCE3B deletion yielded high statistical significance (OR = 1.29, 95%CI = 1.19-1.40, P = 3.32E-10).

Finally, suggestive evidence for association was found for rs4112788 in another genome-wide association scan by Ellinghaus et al 2010 [120]. They used a German cohort involving 472 cases and 1146 healthy controls as discovery sample (OR = 0.76, 95%CI = 0.64-0.89, P = 6.36E-04).

Discussion of the existing meta-analysis and additional studies. In summary, there was strong evidence for the LCE gene cluster to be a psoriasis susceptibility locus. The said finding was replicated by several case-control studies, three genome-wide association scans and a comprehensive meta-analysis. Still, most studies were performed on cohorts from European ancestry.

Only the genome-wide association scan by Zhang et al 2009 [557] and the case-control study of Riveira-Munoz et al 2010 [399] provided evidence of association in Chinese populations while there was no association in Mongolian and Japanese cohorts [399].

Due to a small number of studies, data on psoriatic arthritis was not able to give a comprehensive picture. One out of three studies, however, found evidence for a relation of the LCE locus with psoriasis and additional joint involvement. Further studies are warranted to evaluate this finding.

4.2.8. IL13 variant rs20541

That cytokines play an important role in the pathogenesis of psoriasis is a long known fact. As a consequence, the gene encoding interleukin-13 on chromosome 5q31 is a potential candidate for psoriasis susceptibility (see section 4.1.2). The initial *PubMed* search identified seven studies dealing with the association of IL13 polymorphisms and psoriasis. Apart from rs848 and rs1800925 which had been analysed two times each, rs20541 was the most frequently investigated polymorphism. There was sufficient case-control data to perform a meta-analysis.

Studies excluded from the meta-analysis. A review article by Duffin et al 2009 [115] summarized associations of genetic variants in cytokines with psoriasis. It involved IL13 which had been investigated twice up till then. In addition, a case-control study by Chang et al 2008 [73] reported a significant association between IL13 rs20541 and psoriasis in three independent sample sets counting a total of 1446 patients and 1432 controls. However, no genotyping data could be extracted as the article was not publicly available.

Studies included in the meta-analysis. The remaining case-control studies comprise 14 cohorts with 9577 cases and 12760 controls included in the meta-analysis. For each study the leading author, year of publication, country, clinical variant of psoriasis, numbers and variant allele frequencies of patients and controls, mean age at onset (with standard deviation or range) and percentage of male patients for all cohorts are reported in Table 4.8.

There are several aspects to be considered with respect to study characteristics. For example, the majority of study populations were from European descent residing in European countries, North America or Canada. Only the publication by Chang et al 2007 [77] provided data on two Taiwanese cohorts with Asian ancestry. No other than European and Asian ethnicities were included in the meta-analysis. Relating to gender, the percentage of male patients ranged from 44.4% to 72.4%.

Concerning psoriasis phenotypes, there were several mixed psoriasis cohorts including subjects with and without joint involvement with the respective percentages of psoriatic arthritis ranging between 16% ad 82%. In addition, there were two pure psoriatic arthritis samples, one psoriasis vulgaris sample and two unspecified samples.

Most publications gave information on the mean age at onset. It was rather low whenever provided, ranging from 22.7 years to 30.8 years. Chang et al 2007 [77] stated the percentage of how many subjects suffered from each onset type in their two cohorts. While there were more early-onset psoriasis cases in the psoriatic arthritis cohort (74%), the distribution of early- and late-onset psoriasis was balanced in the psoriasis vulgaris cohort. A direct comparison between the two onset types was not performed though.

Results of the meta-analysis. The meta-analysis of the IL13 rs20541 G allele and psoriasis yielded an association estimate of 1.23 (95%CI = 1.14-1.33, $P < 0.0001$) (Figure 4.20). The between-study heterogeneity was high which was confirmed by Cochran Q

Table 4.8.: Characteristics of studies included in meta-analysis of IL13 rs20541 polymorphism in psoriasis

			Numbers		Frequency			
Study [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**Onset**	**Male**
Strange 2010 [453]	UK/Ire (E)	P	2262	5667	-	-	-	-
Duffin 2009 [114]	US (E)	P	334	458	81.6	80.3	22.7 (14.4)	53.6
Chang 2007 [77] $^{\Phi}$	Taiwan (A)	PV (49% P1)	170	210	63.2	67.6	$\leq 40 \leq$	72.4
Duffin 2009 [114]	US (E)	PA	181	458	86.2	80.3	25.9 (14.3)	44.4
Chang 2007 [77] $^{\Phi}$	Taiwan (A)	PA (74% P1)	102	210	73.5	67.6	$\leq 40 \leq$	52.0
Nair-1 2009 [318]	Europe (E)	PPA (27% PA)	1359	1400	83.2	78.3	26.1	48.3
Nair-2 2009 [318]	US (E)	PPA (16% PA)	1642	1101	83.0	77.5	30.8	46.3
Nair-3 2009 [318]	Canada (E)	PPA (82% PA)	368	358	82.7	80.1	28.3	47.8
Nair-4 2009 [318]	Canada (E)	PPA (72% PA)	691	217	82.2	76.5	29.4	59.9
Nair-5 2009 [318]	Germany (E)	PPA (17% PA)	718	1464	80.9	78.1	25.1	52.1
Nair-6 2009 [318]	US (E)	PPA (34% PA)	302	500	81.9	81.4	28.0	49.0
Li-1 2008 [281]	US (E)	PPA	467	460	84.6	80.3	28 (17)	45.0
Li-2 2008 [281]	US (E)	PPA	498	498	83.1	80.4	29 (15)	45.0
Li-3 2008 [281]	US (E)	PPA	481	424	84.7	80.8	28 (16)	52.8
Total			9577	12760	80.8	78.3		

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Freq, frequency of the IL13 rs20541 G allele in %; Clinic, clinical psoriasis variants in patients; *, percentage of early-onset psoriasis (P1) or psoriatic arthritis (PA) in brackets; Onset, mean age at onset with standard deviation or range in brackets; $\leq 40 \leq$, patients with onset before and after 40 years (early- and late-onset psoriasis) involved; Male, percentage of male patients in %; P, psoriasis without further specification; PV, psoriasis vulgaris; PA, psoriatic arthritis; PPA, psoriasis without further specification and psoriatic arthritis; $^{\Phi}$, these studies use the same control subjects; - , data not provided in the article;

test (P = 0.0489) and which was reflected by odds ratios ranging from 0.82 to 1.53. Consequently, a random effects model was applied to calculate the pooled estimate. Egger's regression test which showed no deviation from the symmetry assumption (P = 0.9639) argued against publication bias (Figure 4.21).

Even if the distribution of significant and non-significant results is rather balanced, the overall analysis favors a relation between the IL13 polymorphism and psoriasis. The highest association estimate was achieved by a psoriatic arthritis cohort, but as most of the samples were mixed no stratification by psoriasis phenotype was feasible. Yet neither cohorts with high percentage nor low percentage of psoriasis arthritis did stick out from the analysis (compare Table 4.8 and Figure 4.20). The same applies for the mainly early-onset cohort of Chang et al 2007 [77].

Regarding different ethnicities, none of the Asian samples reached significance while eight out of twelve European samples reported a positive association. Yet data is insufficient to propose the hypothesis of a ethnicity-dependent association. In addition, the allele frequency in the Taiwanese control population of Chang et al 2007 [77] was only marginally lower than in the populations from European descent. The mean frequency of the G allele over all ethnicities was 78.3%.

Discussion of the meta-analysis. The significant outcome of the meta-analysis favors a relation of the IL13 rs20541 variant to psoriasis. This is in conformity with the result of an excluded case-control study by Chang et al 2008 [73] which had reported a significant association in three independent sample sets. In the meta-analysis, the highest association estimate was achieved for a psoriatic arthritis cohort. In addition, most mixed samples involved psoriatic arthritis as well, but data was insufficient to validate the hypothesis of a phenotype-dependent association. The same applies for a putative dependence on onset or ethnicity. Yet both Asian cohorts showed negative results.

In summary, one can suggest a significant association of the Il13 polymorphism rs20541 with psoriasis and/or psoriatic arthritis in populations from European descent. Yet further analyses supported the suspected dependency from joint involvement as interleukin-13 was not expressed in lesional psoriatic skin but in the synovial fluid of psoriatic arthritis [446].

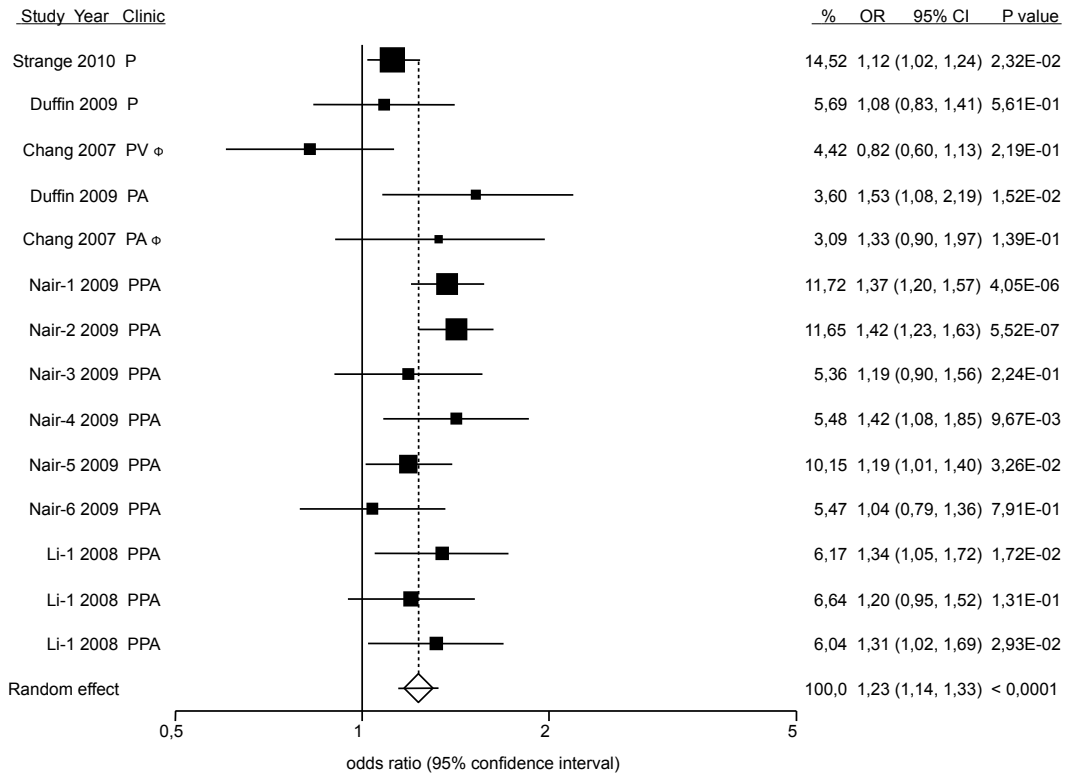


Figure 4.20.: Association of IL13 rs20541 G allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.8.

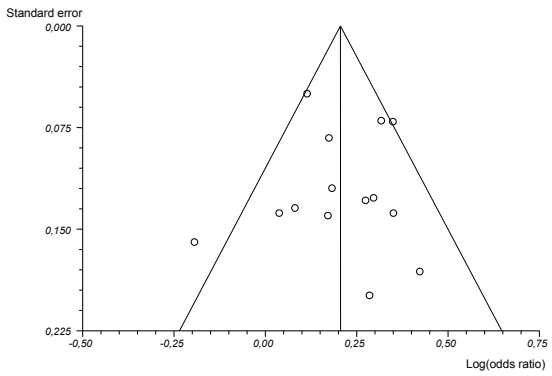


Figure 4.21.: Funnel plot showing log(OR)s and standard errors for the association of IL13 rs20541 G allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test, P = 0.9639.

4.2.9. IL12B variants rs3212227 and rs6887695

Since cytokines are believed to play an important role in the pathogenesis of psoriasis, genes linked to the production or modulation of such cytokines are well-studied candidate genes. This holds true for IL12B on chromosome 5q31.1-q33.1 which encodes the common p40 subunit of interleukin-12 and interleukin-23. While interleukin-12 is important for IFN-γ induction and Th1 cell differentiation, interleukin-23 promotes Th17 cell differentiation (see section 4.1.2).

The single nucleotide polymorphism rs3212227 is the best-studied genetic variant. Since Tsunemi et al 2002 [486] had investigated this putative association, eleven other study groups aimed to replicate the finding. In addition to that, the genetic variant rs6887695 was discovered in a genome wide association scan by Cargill et al 2007 [69].

Studies excluded from the meta-analyses of rs3212227 and rs6887695. In 2008, Zell et al [552] published a short review on the associations of Crohn's disease and psoriasis with IL12B polymorphisms. Both rs3212227 and rs687695 had shown significant results in association studies until then.

A review by Duffin et al 2009 [115] presented an even larger overview of psoriasis risk genes including IL12B and its genetic variants. In addition to summarizing genetic predispositions, a case-control analysis on the homozygous rs3212227 AA genotype in 497 cases and 450 controls was carried out. They stratified the results for the presence of HLA-Cw*0602 and found that the estimated risk was higher if the HLA-C allele was present (OR = 6.17, 95%CI = 4.01-9.49, P < 0.0001), but still remained significant for rs3212227 alone (OR = 1.74, 95%CI = 1.25-2.44, P = 0.001). As no corresponding genotyping data was provided, an inclusion into the meta-analysis was not possible.

Studies included in the meta-analyses of rs3212227 and rs6887695. Finally, ten studies involving 16 cohorts met the inclusion criteria for rs3212227 and eight studies involving 13 cohorts for rs6887695. A total of 8475 psoriasis patients and 11968 healthy controls were included in the meta-analysis of rs3212227, while there were 8395 cases and 11031 controls for rs6887695. Some basic information and characteristics of the study samples are listed in Table 4.9.

Regarding ethnicity, all studies investigated Asian or Caucasian populations. There were eight cohorts from European countries, five from North America and five from Asia. The age distribution showed a large variation, ranging form birth to approximately 91 years. Yet corresponding data were missing from two thirds of the study samples.

Still, most of the studies stated the mean age at disease onset instead. While the cohorts of Cargill et al 2007 [69] showed a rather high mean age at onset, all cases of Smith et al 2008 [437] had early-onset psoriasis. Similarly, at least 93% of the patients with psoriasis vulgaris of Huffmeier et al 2009 [202] had an early onset of disease.

Concerning deviating clinical psoriasis variants, most studies used mixed samples involving rare phenotypes like guttate psoriasis or did not specify the phenotype. Yet the were some separate investigations on psoriasis vulgaris and psoriatic arthritis, making an evaluation of dependency on diseases phenotype possible.

Table 4.9.: Characteristics of studies included in meta-analyses of IL12B variants rs3212227 and rs6887695 in psoriasis

			Numbers		Frequencies rs3212227		Frequencies rs6887695			
Study [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**P**	**C**	**Age^{+}**	**Male**
Wu 2010 [538]	China (A)	P	578	1422	-	-	65.3	58.3	-	58.1
Nair 2010 [323]	Thai (A)	P	206	114	62.2	51.0	59.7	52.6	(0-81)	58.0
Smith 2008 [437] $^{\Omega}$	UK (E)	P1	597	4681	84.6	80.6	73.3	68.2	+	53.6
Capon-1 2007 [65]	UK (E)	P	302	281	85.4	82.0	-	-	52.1 (23-86)	65.4
Capon-2 2007 [65]	UK (E)	P	517	491	83.9	79.8	-	-	44.1 (9-91)	42.4
Huffmeier 2009 [202] $^{\Phi 1}$	Ger (E)	PV (93%)	1114	937	85.0	79.1	76.4	69.4	48.2 (13.4)$^{+}$	62.0
Chang 2007 [77] $^{\Phi 2}$	Taiwan (A)	PV (49%)	170	210	62.9	55.2	-	-	52.1 (7-84)	72.4
Tsunemi 2002 [486]	Japan (A)	PV	143	100	60.1	50.5	-	-	-	-
Huffmeier 2009 [202] $^{\Phi 1}$	Ger (E)	PA	748	937	84.9	79.1	77.2	69.4	+	61.8
Filer 2008 [134] $^{\Omega}$	UK (E)	PA	520	4681	85.4	80.6	74.5	67.4	-	-
Liu 2008 [287]	UK (E)	PA	576	480	-	-	78.7	72.0	-	-
Chang 2007 [77] $^{\Phi 2}$	Taiwan (A)	PA (74%)	102	210	59.8	55.2	-	-	45.6 (19-79)	52.0
Liu 2008 [287]	US (E)	PVA	810	1256	84.2	80.1	77.9	70.6	-	-
Nair-1 2008 [320]	US (E)	PVAG	1441	1422	85.6	76.7	76.0	67.2	-	-
Nair-2 2008 [320]	Ger (E)	PVAG	359	1094	85.7	80.9	76.7	70.7	-	-
Cargill-1 2007 [69]	US (E)	PPA	467	460	85.7	79.1	74.6	68.1	+	45.0
Cargill-2 2007 [69]	US (E)	PPA	498	498	86.3	77.7	75.8	66.7	+	45.0
Cargill-3 2007 [69]	US (E)	PPA	481	424	83.3	78.8	74.9	69.2	+	52.8
Total rs3212227			8475	11968	79.1	73.2				
Total rs6887695			8395	11031			73.9	66.7		

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Frequencies, frequencies of the rs3212227 A allele and the rs6887695 C allele in %; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Age, mean age of patients with standard deviation or range in brackets; Male, percentage of male patients in %; P, psoriasis without further specification; P1, early-onset psoriasis (Type 1); PV, psoriasis vulgaris; PA, psoriatic arthritis; PVA, psoriasis vulgaris and psoriatic arthritis; PVAG, psoriasis vulgaris, psoriatic arthritis and guttate psoriasis; PPA, psoriasis without further specification and psoriatic arthritis; $^{\Phi 1-2}$, these studies use the same control subjects, respectively; $^{\Omega}$, these studies included less control subjects in the analysis of rs6887695 (Smith 2008: 2924, Filer 2008: 2260); $^{+}$, mean age at onset in Table 4.10 on page 116; - , data not provided in the article;

Results of the meta-analysis of rs3212227. Only two of the 16 reports did not report a significant result for the association between IL12B rs321227 A allele and psoriasis. These were the discovery cohort (1) of Capon et al 2007 [65] and the psoriatic arthritis cohort of Chang et al 2007 [77]. The remaining studies, however, suggested an increased risk conceded by the rs3212227 A allele.

The meta-analysis on all psoriasis phenotypes and all ethnicities yielded significant evidence of association (OR = 1.47, 95%CI = 1.40-1.56, $P < 0.0001$). A fixed effects model was considered appropriate for the calculation, as Cochran Q test did not reveal significant heterogeneity between the studies ($P = 0.2406$). The individual odds ratios ranged between 1.21 and 1.81, supporting the impression of low heterogeneity. The results of the meta-analysis are visualized in Figure 4.22 where each study is characterized by its first author, year of publication and clinical psoriasis variant. In addition, the individual results and their weights (%) in the meta-analysis are given. No publication bias was detected by Egger's regression test ($P = 0.2392$) nor by funnel plot analysis (Figure 4.23).

As there were twelve studies on populations from European descent and four studies on Asian populations, additional meta-analyses according to ethnicity were performed. This resulted in odds ratios of 1.48 (95%CI = 1.40-1.57, $P < 0.0001$) and 1.40 (95%CI = 1.18-1.66, $P < 0.0001$) for subjects with European and Asian descent, respectively (Figures 4.24 and 4.25). As the values differed only marginally from the result achieved by the overall meta-analysis, a similar pattern of inheritance for both ethnicities can be discussed.

Yet the mean frequencies of the IL12B rs3212227 A allele revealed wide differences between ethnic groups. Only 52.2% of the Asian controls carried the A allele whereas 79.5% of the Europeans did, giving an average value of 76.9% for all control populations. This observation implies that the rs3212227 A allele is more common in populations from European descent.

As most studies were carried out on samples with mixed clinical psoriasis variants, no additional meta-analyses were performed according to phenotypes. Yet the exclusive psoriasis vulgaris and psoriatic arthritis samples did not stand out from the overall meta-analysis implying an association independent from joint involvement. Concerning rare phenotypes, there were no specific samples on guttate psoriasis or palmoplantar pustulosis.

As none of the studies investigated early- and late-onset psoriasis separately, no quantified statement on differences in heredity according to age at onset can be given. Yet one can observe that the study by Smith et al 2008 [437] consisting of early-onset subjects only, did not stick out from the combined analysis. The same applied to the mainly early-onset psoriasis vulgaris group of Huffmeier et al 2009 [202] (Figure 4.22).

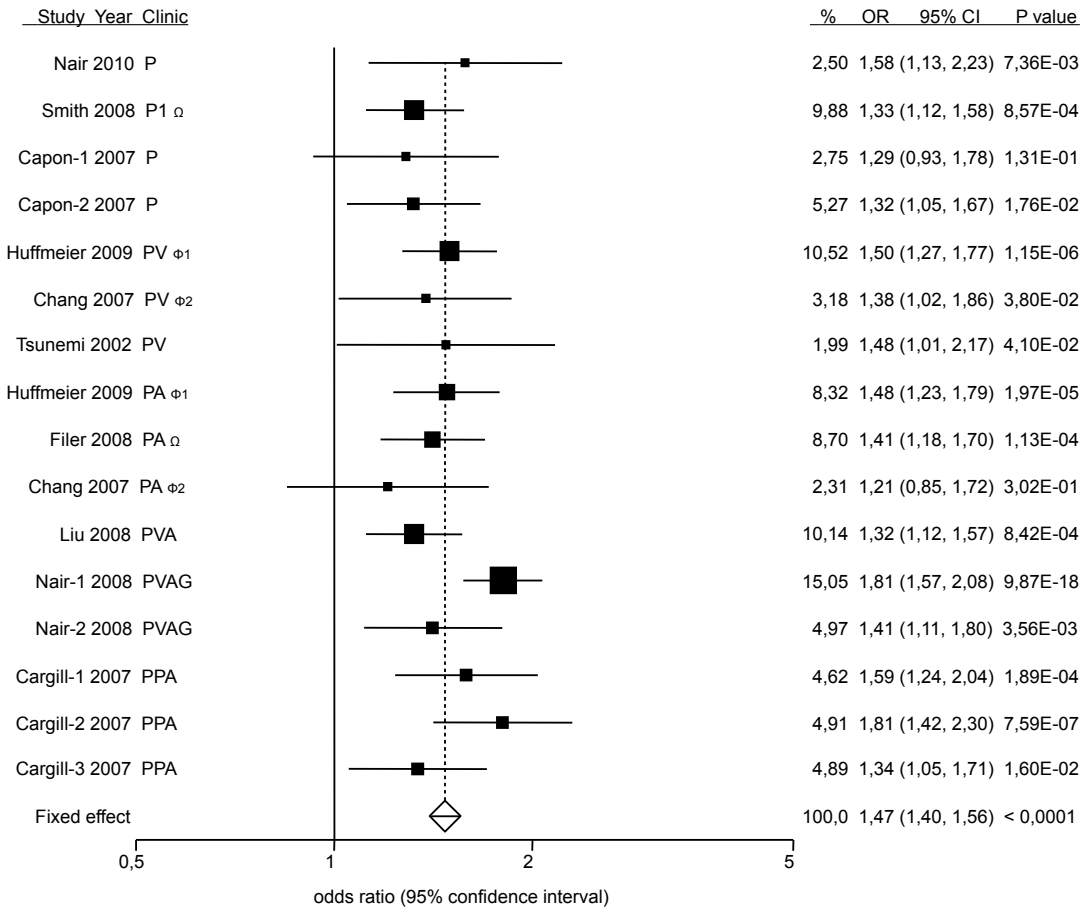


Figure 4.22.: Association of IL12B rs3212227 A allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.9.

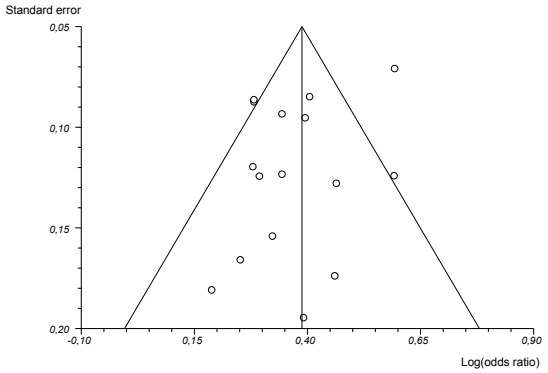
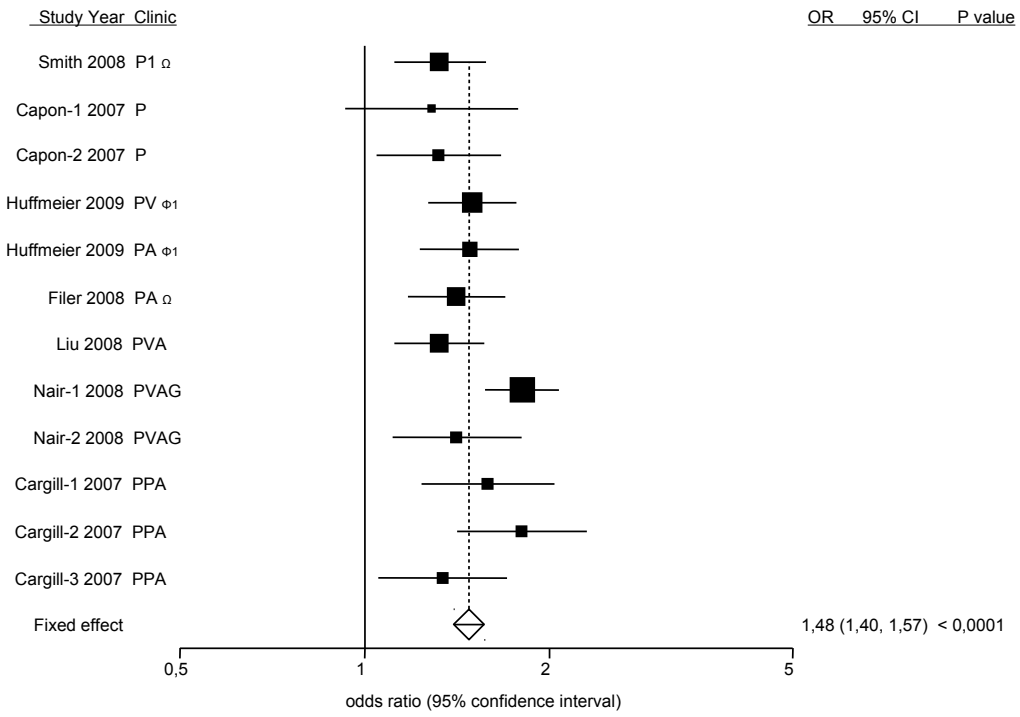
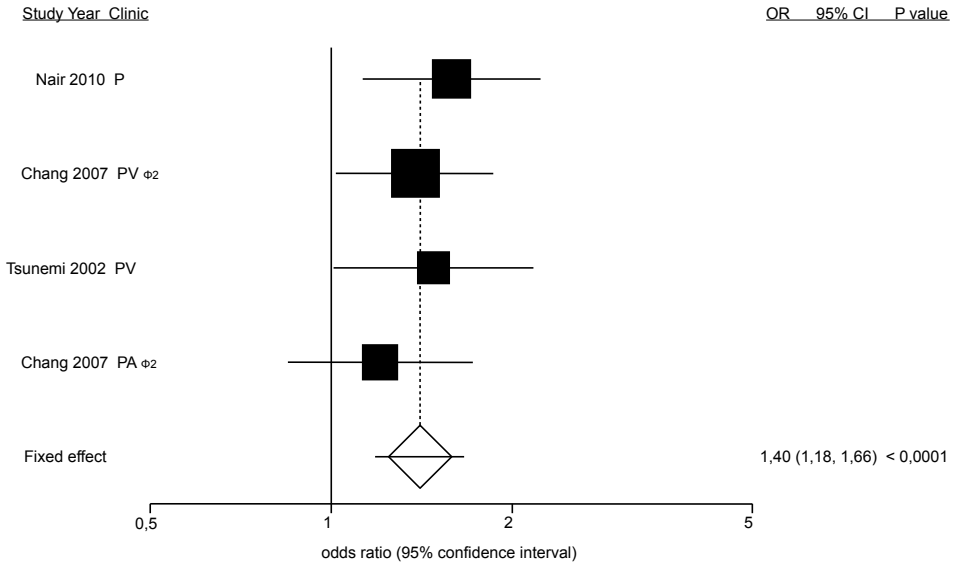


Figure 4.23.: Funnel plot showing log(OR)s and standard errors for the association of IL12B rs3212227 A allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.2392.

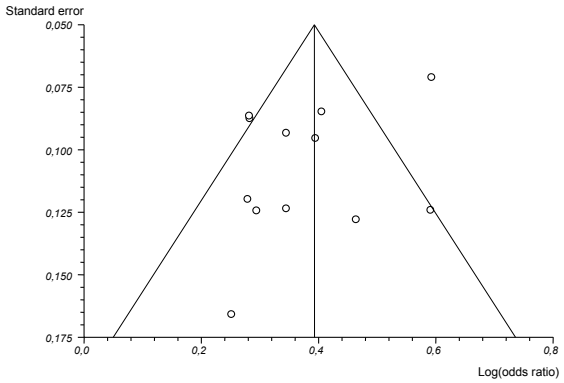


(a) Europe

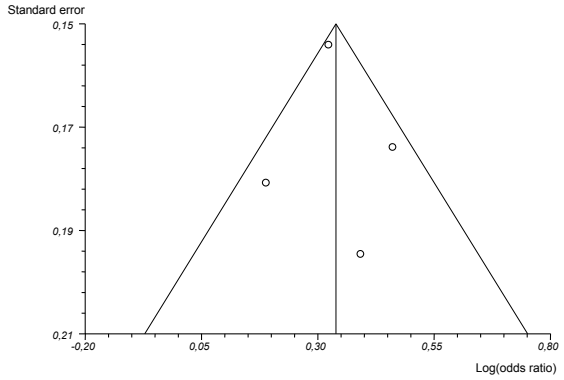


(b) Asia

Figure 4.24.: Association of IL12B rs3212227 A allele with psoriasis in (a) European and (b) Asian populations. Forest plots showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analyses. Abbreviations see Table 4.9.



(a) Europe



(b) Asia

Figure 4.25.: Funnel plots showing log(OR)s and standard errors for the association of IL12B rs3212227 A allele with psoriasis in (a) European and (b) Asian populations. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P values > 0.05; (a) $P = 0.051$; (b) $P = 0.1437$.

Results of the meta-analysis of rs6887695. Even if there were less replication studies for the rs6887695 variant, the total number of investigated subjects was equally high. In fact, the meta-analysis counted only 80 patients less. Only one out of 13 reports failed to confirm a significant association between the IL12B rs6887695 C allele and psoriasis. All remaining studies affirmed an increased risk conceded by the rs6887695 C allele.

The meta-analysis on all psoriasis phenotypes and all ethnicities yielded significant evidence of association (OR = 1.42, 95%CI = 1.36-1.49, P < 0.0001). Here, too, a fixed effects model was applied as the result of Cochran Q test remained insignificant (P = 0.8585). Low between-study heterogeneity was reflected by individual odds ratios reaching from 1.28 to 1.55. Figure 4.26 provides a forest plot showing individual results and their weights (%) together with the combined association estimate. Neither Egger's regression test (P = 0.4054) nor funnel plot analysis indicated publication bias (Figure 4.27).

As there were eleven studies on populations from European descent (residing in Europe or the United States) and merely two studies on Asian populations, a separate meta-analysis was performed for European populations. An association value of 1.43 (95%CI = 1.36-1.50, P < 0.0001) was obtained applying a fixed effects model, as there was no evidence of significant heterogeneity between the studies (P = 0.7966). It is not much of a surprise that the result hardly differs from the overall meta-analysis as Asian subjects only made up only 12%. Still, the mean frequency of the IL12B rs6887695 C allele differed between ethnic groups. Frequencies of 55.5% in Asian controls versus 68.9% in European controls indicate that the C allele is slightly more common in European populations.

Given that most studies used mixed or unspecified psoriasis sample sets, an additional meta-analyses according to phenotype was only feasible for the self-contained group of psoriatic arthritis. The result showed hardly a deviation from the combined meta-analysis (OR = 1.43, 95%CI = 1.30-1.58, P < 0.0001), thus not indicating an association to psoriasis with joint involvement in particular.

As none of the studies provided separate data on early- and late-onset psoriasis patients, an evaluation of dependency on age at onset by direct comparison was not possible. The observation that the early-onset study of Smith et al 2008 [437] showed the lowest association estimate does not seem substantially as the mainly early-onset psoriasis vulgaris group of Huffmeier et al 2009 [202] did not stick out from the combined analysis (Figure 4.26). Consequently, an influence imparted by age at onset is not very probable, but cannot be ruled out due to insufficient data.

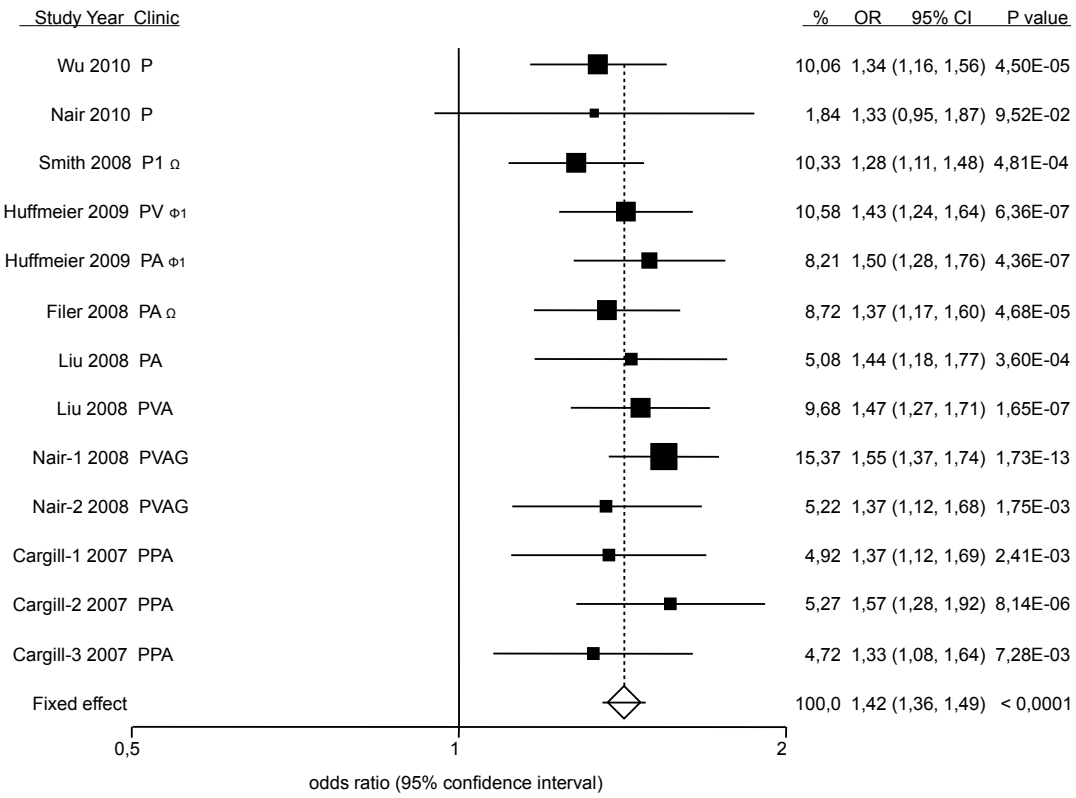


Figure 4.26.: Association of IL12B rs6887695 C allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.9.

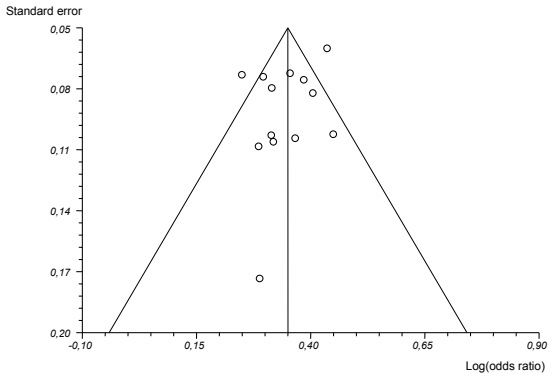


Figure 4.27.: Funnel plot showing log(OR)s and standard errors for the association of IL12B rs6887695 C allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.4054.

Discussion of the meta-analyses of rs3212227 and rs6887695. The performed meta-analyses supported significant associations of both IL12B variants, rs3212227 and rs6887695, with an increased risk for psoriasis phenotypes. Individuals carrying the rs3212227 A allele were shown to have a 1.47 fold risk of developing psoriasis, while the risk for those carrying the rs6887695 C allele was 1.42 times higher. Between-study heterogeneity was practically non-existent with almost all case-control studies being able to detect an association of the IL12B polymorphisms and psoriasis. The remaining non-significant studies showed low numbers of cases and controls, making an underestimation of the effect due to small sample sizes likely.

Relating to ethnicity, there were substantial differences between allele frequencies in Caucasian populations (79.5%) and Asian populations (52.2%) for rs3212227, and less pronounced for rs6887695. Yet the association per se did not seem reliant on ethnicity, showing equally high association estimates. Concerning distinct clinical types of psoriasis, no influence on association estimates was noticed either. Especially psoriasis vulgaris and psoriatic arthritis showed a similar degree of association. Hence it might be deduced that both the IL12B rs3212227 A allele and the rs6887695 C allele contribute to psoriasis risk regardless of clinical phenotype and ethnicity.

Certainly, this conclusion has to be treated with caution as the real distribution of psoriasis variants in the sample sets remained unclear. Some studies did not specify the psoriasis subtype while others included subjects with different subtypes not stating proportions. For example, the percentage of the rare phenotype guttate psoriasis was not apparent. Furthermore, the proportion of patients suffering from accompanying arthritis seemed to be very high. This is important, as different patterns in the genetics of psoriasis with only skin lesions and with additional joint lesions are discussed.

An evaluation of dependency on age at onset by direct comparison was not possible, as none of the studies provided separate data on early- and late-onset psoriasis. Yet an early-onset cohort showed the lowest association estimate. Regarding a putative dependence on ethnicity, populations from other than European or Asian descent remain to be investigated as the meta-analyses relate only the these two ethnicities. An influence by gender was not observed.

The question if IL12B is a risk factor independent from HLA-C, was investigated by the excluded study of Duffin et al 2009 [115]. They performed a case-control analysis on the homozygous rs3212227 AA genotype and stratified the results for the presence of HLA-Cw*0602, finding that the estimated risk was higher if the HLA-C allele was present but remained significant if not.

In addition to association analyses, the relevance of IL12B as a candidate gene for psoriasis was examined by other research protocols. For example, an over-expression of p40 mRNA for IL12B was observed in lesional skin of patients with psoriasis vulgaris, indicating a correlation [32, 271]. In addition, the common p40 chain of interleukin 12 and interleukin 23 was successfully tested as a new target for monoclonal antibody therapy [330, 258].

4.2.10. IL23R variants rs11209026 and rs7530511

The IL23R gene on chromosome 1p31.3 encodes part of a cytokine receptor involved in the interleukin-23 pathway. The said interleukin in turn contributes to the pathogenesis of psoriasis by inducing Th17 cell differentiation (see section 4.1.2). It moved to the center of interest when Cargill et al 2007 [69] discovered that the SNPs rs11209026 and rs7530511 were correlated with an increased risk to develop psoriasis in a genome-wide association study. Since then, enough case-control data was accumulated to perform a comprehensive meta-analysis for both polymorphisms.

Studies excluded from the meta-analyses of rs11209026 and rs7530511. There were two review articles dealing with the IL23R polymorphisms. While Zell et al 2008 [552] discussed the associations of Crohn's disease and psoriasis with IL12B and IL23R, Duffin et al 2009 [115] provided an even larger overview on psoriasis risk genes including the said candidate. In addition, Garcia et al 2008 [147] carried out a fine-mapping of the IL23R locus on chromosome 1p31.3.

Studies included in the meta-analyses of rs11209026 and rs7530511. Nine case-control studies containing 16 cohorts with a total of 9193 patients and 14258 healthy controls met the inclusion criteria for the meta-analysis of rs11209026, while five studies containing 11 cohorts with a total of 6720 cases and 11414 controls were included in the meta-analysis of rs7530511. For each study the leading author, year of publication, country, clinical psoriasis variant, number of patients and controls, allele frequencies, mean age at onset and percentage of male patients are reported in Table 4.10.

Regarding ethnicity, all studies were carried out in populations from European descent. In detail, there were cohorts from the United States, Canada, the United Kingdom, Germany and Finland. The percentage of male patients varied from 42.2% to 85.0%.

Half of the studies gave information on mean ages at disease onset, mostly ranging between 26.9 and 29.5 years. Only the early-onset cohort of Smith et al 2008 [437] and mainly early-onset cohort of Huffmeier et al 2009 [202] showed lower ages at onset of 19.8 and 23.2 years, respectively.

Concerning deviating clinical psoriasis variants, most studies used mixed samples involving rare phenotypes like guttate psoriasis or did not specify the phenotype. Yet the were some separate investigations on psoriasis vulgaris and psoriatic arthritis, making an evaluation of dependency on diseases phenotype possible.

Relating to genotyping methods, the *TaqMan assay* [202, 65] and the *Sequenom MassArray system* [287, 134, 384] were most frequently used. Only Cargill et al 2007 [69] used a different approach in their genome-wide association scan and Smith et al 2008 [437] did not mention the applied genotyping technique at all.

Results of the meta-analysis of rs11209026. The overall meta-analysis supported a protective effect conceded by the A allele (OR = 0.62, 95%CI = 0.57-0.68, $P < 0.0001$), as indicated by the positive results of 13 out of 16 case-control studies. A fixed effects model was applied as Cochran Q test did not reveal significant heterogeneity between the

Table 4.10.: Characteristics of studies included in meta-analyses of IL23R variants rs11209026 and rs7530511 in psoriasis

			Numbers		Frequencies rs11209026		Frequencies rs7530511			
Study [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**P**	**C**	**Onset^{+}**	**Male**
Smith 2008 [437] $^{\Omega}$	UK (E)	P1	595	2911	3.7	5.9	8.0	13.0	19.8	53.6
Capon-1 2007 [65]	UK (E)	P	318	288	2.2	7.2	-	-	+	65.4
Capon-2 2007 [65]	UK (E)	P	519	528	4.5	6.9	-	-	+	42.4
Huffmeier 2009 [202] $^{\Phi}$	Ger (E)	PV (93%)	1114	937	3.9	7.2	12.9	13.3	23.2 (11.9)$^{+}$	85.0
Rahman-1 2009 [384]	Can (E)	PA	247	228	4.1	7.6	12.2	12.7	29.5 (14.5)	50.6
Rahman-2 2009 [384]	Can (E)	PA	249	248	4.0	6.8	11.5	10.3	26.9 (11.4)	42.2
Huffmeier 2009 [202] $^{\Phi}$	Ger (E)	PA	748	937	4.6	7.2	11.6	13.3	28.8 (13.3)	61.8
Filer 2008 [134] $^{\Omega}$	UK (E)	PA	520	2260	5.0	6.6	9.8	11.5	-	-
Liu 2008 [287]	UK (E)	PA	576	480	4.3	7.9	-	-	-	-
Subtotal			2340	4153	4.4	7.2	11.3	12.0		
Einarsdottir 2009 [117]	Fin (E)	PVAG	250	292	2.2	3.1	-	-	-	-
Liu 2008 [287]	US (E)	PVA	810	1256	3.9	6.6	-	-	-	-
Nair-1 2008 [320]	US (E)	PVAG	1442	1417	5.5	6.9	11.1	12.5	-	-
Nair-2 2008 [320]	Ger (E)	PVAG	359	1094	4.3	7.5	12.3	15.7	-	-
Cargill-1 2007 [69]	US (E)	PPA	467	460	4.4	6.0	10.3	14.6	28 (17)	45.0
Cargill-2 2007 [69]	US (E)	PPA	498	498	5.1	7.7	10.0	11.4	29 (15)	45.0
Cargill-3 2007 [69]	US (E)	PPA	481	424	3.5	6.6	10.8	13.0	28 (16)	52.8
Total rs11209026			9193	14258	4.1	6.7				
Total rs7530511			6720	11414			11.0	12.8		

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Frequencies, frequencies of the rs11209026 A allele and the rs7530511 T allele in %; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Onset, mean age at onset with standard deviation or range in brackets; Male, percentage of male patients in %; P, psoriasis without further specification; P1, early-onset psoriasis (Type 1); PV, psoriasis vulgaris; PA, psoriatic arthritis; PVAG, psoriasis vulgaris, psoriatic arthritis and guttate psoriasis; PVA, psoriasis vulgaris and psoriatic arthritis; PPA, psoriasis without further specification and psoriatic arthritis; $^{\Phi}$, these studies use the same control subjects, respectively; $^{+}$, mean age of patients in Table 4.9 on page 106; - , data not provided in the article;

studies (P = 0.5323) with individual odds ratios ranging from 0.31 to 0.78. The results of the meta-analysis are visualized in Figure 4.28 where each study is characterized by its first author, year of publication and clinical psoriasis variant. In addition, the individual results and their weights (%) in the meta-analysis are given. A borderline significant publication bias was detected by Egger's regression test (P = 0.0462), while the funnel plot analysis provides a nearly symmetrical shape (Figure 4.29).

As all studies had been carried out on populations with European descent, no stratification by ethnicity was indicated. In addition, allele frequencies in control populations were rather homogeneous within European countries, the United States and Canada. They ranged from 5.9% to 7.9% with exception of the Finnish control population, which showed a lower frequency of only 3.1%.

As most studies used mixed or unspecified samples, only one additional meta-analysis

was performed on a self-contained group of psoriatic arthritis samples. The result was similar to the overall meta-analysis (OR = 0.62, 95%CI = 0.52-0.74, P < 0.0001), not indicating a stronger association with psoriatic arthritis in particular.

None of the studies provided separate data on early- and late-onset psoriasis, which made a quantified statement on differences in heredity according to age at onset impossible. The only relevant observation was that data of Smith et al [437] and Huffmeier et al 2009 [202] involving exclusively or mainly early-onset psoriasis (93%), respectively, did not stick out substantially (Figure 4.28).

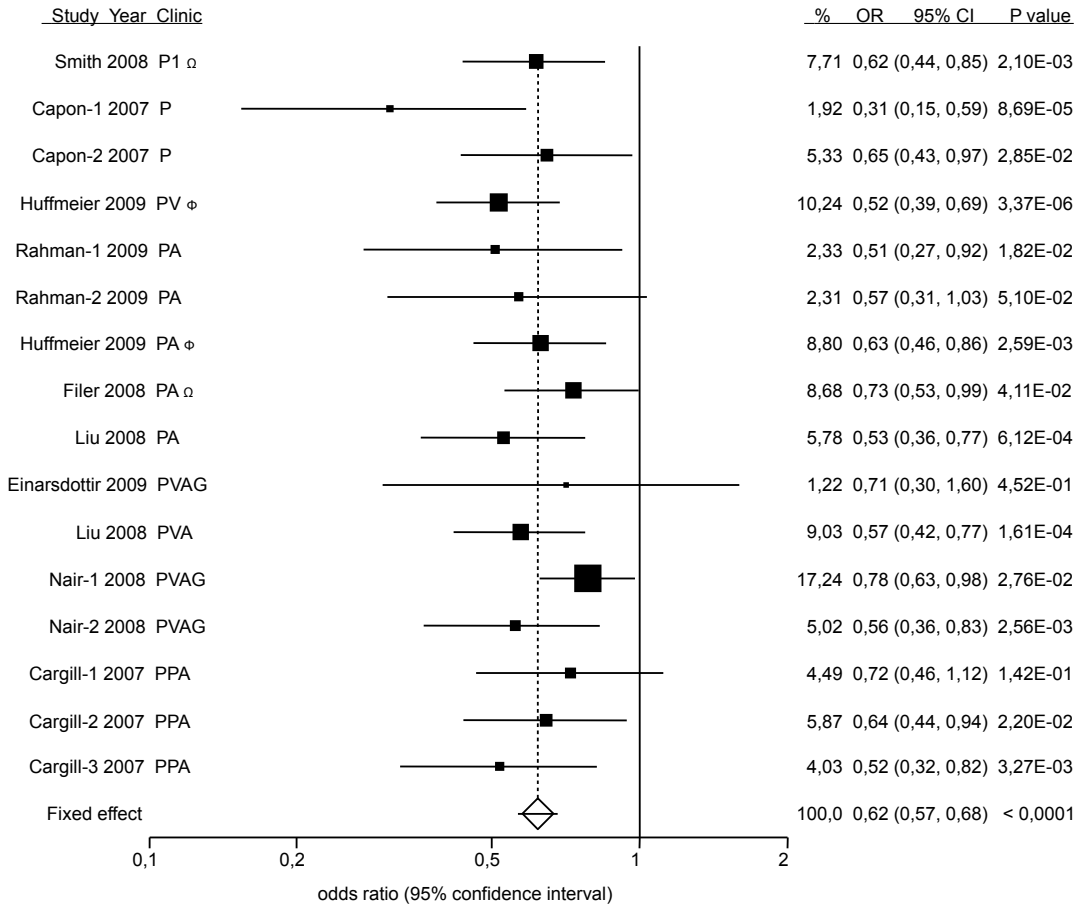


Figure 4.28.: Association of IL23R rs11209026 A allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.10.

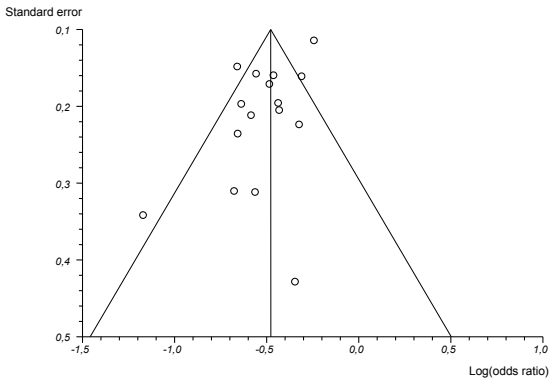


Figure 4.29.: Funnel plots showing log(OR)s and standard errors for the association of IL23R rs11209026 A allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.0462.

Results of the meta-analysis of rs7530511. There were less publications for the rs7530511 variant of IL23R and only three out of eleven reports confirmed a significant association between the IL12B rs7530511 T allele and psoriasis. Nevertheless, the overall meta-analysis provided significant evidence of association (OR = 0.83, 95%CI = 0.77-0.89, P < 0.0001). Here, too, a fixed effects model was applied as Cochran Q test did not show between-study heterogeneity (P = 0.1156). The results of the meta-analysis are visualized in Figure 4.30 where each study is characterized by its first author, year of publication and clinical psoriasis variant. In addition, the individual results and their weights (%) in the meta-analysis are given. No publication bias was detected using Egger's regression test (P = 0.8327) and the funnel plot has a symmetrical shape (Figure 4.31).

As all studies had been performed on populations of European descent, no stratification by ethnicity was indicated. The allele frequencies in controls were similar for all countries ranging from 10.3% to 15.7%. Regarding the results for different psoriasis phenotypes, one can observe that all studies on exclusively psoriatic arthritis or exclusively psoriasis vulgaris did not reach statistical significance. In contrast, for mixed samples including psoriatic arthritis and/or psoriasis vulgaris an association was detected. Consequently, no statement about a putative dependence on clinical subtype could be made due to conflicting results.

As none of the studies provided separate data on early- and late-onset psoriasis, no quantified statement about dependence on age at onset could be made either. The only relevant observation was that data of Smith et al 2008 [437] consisting of early-onset subjects showed by far the most significant result. However, the psoriasis vulgaris group of Huffmeier et al 2009 [202] in which the major proportion of patients showed disease onset before the age of 40 did not reach significance (Figure 4.30). Still, a preferential association with early-onset psoriasis cannot be ruled out due to insufficient data.

Discussion of the meta-analyses of rs11209026 and rs7530511. The performed meta-analyses supported a significant association of IL23R variants rs11209026 and rs7530511 with psoriasis. Individuals carrying the rs11209026 A allele had a 0.6 fold decreased risk of developing psoriasis, while the risk for those carrying the rs7530511 T allele was 0.8 times lower. There was almost no heterogeneity between studies, but borderline publication bias was detected for the meta-analysis of rs11209026.

As most samples contained mixed or unspecified phenotypes, no reliable statement on differences in heredity according to clinical subtype could be made. The same is true for a dependency on onset-type as no separate data on early- and late-onset psoriasis was provided. Yet an early-onset cohort showed by far the most significant result. Regarding ethnicity, the positive results of the meta-analyses relate only to populations from European descent. Samples from other ethnic background remain to be investigated. Gender did not seem to have a significant influence.

In addition to association analyses, the relevance of IL23R as a candidate gene for psoriasis was examined by other research protocols. For example, Tonel et al 2010 [479] reported that both interleukin 23 and its receptor (IL23R) were over-expressed in the tissues of psoriasis patients. In addition, they found an interleukin-23 dependent inhibition of psoriasis development in monoclonal antibody treatment [479], while the p40 chain of both interleukin 12 and interleukin 23 had been established as a new therapeutic target earlier [330, 258].

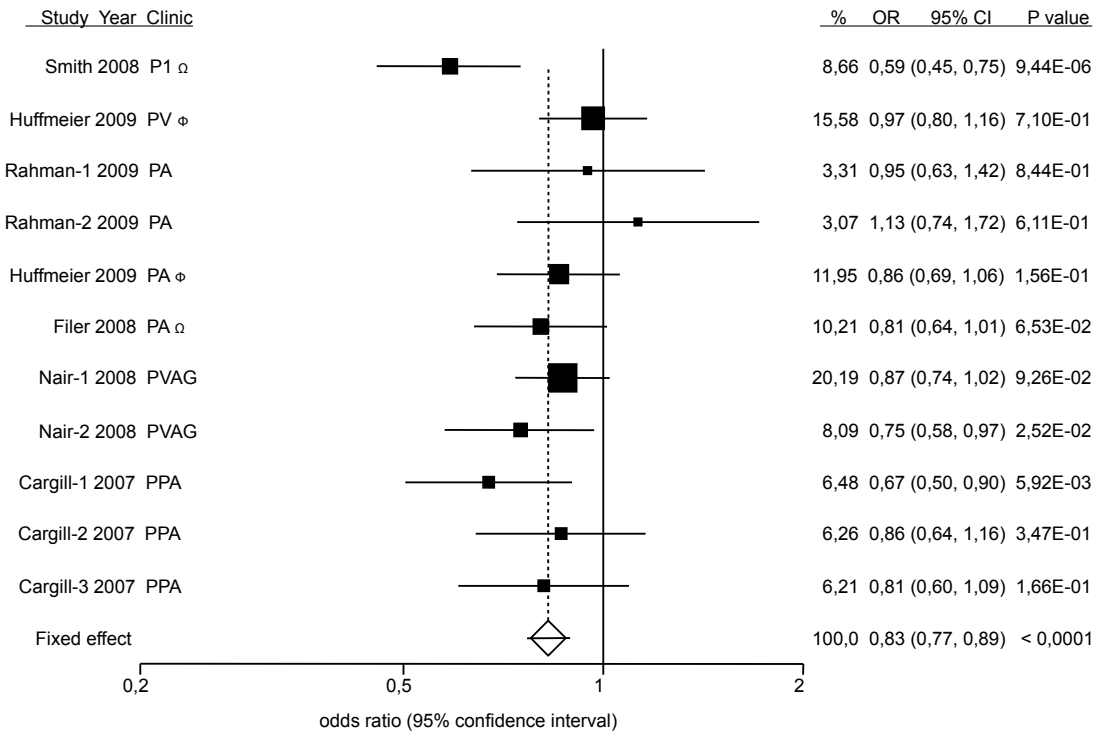


Figure 4.30.: Association of IL23R rs7530511 T allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.10.

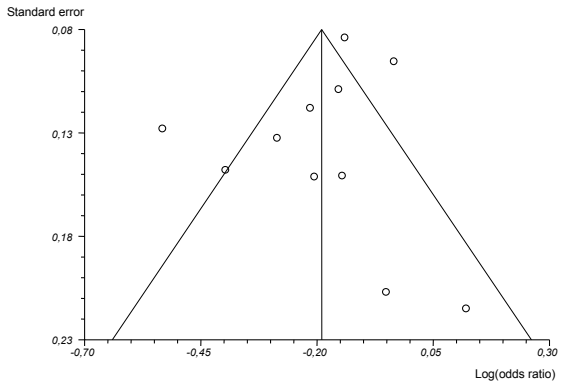


Figure 4.31.: Funnel plots showing log(OR)s and standard errors for the association of IL23R rs7530511 T allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.8327.

4.2.11. MICA triplet repeat $(GCT)_n$

The MICA (MHC class I chain-related A) gene lies 46kb centromeric to HLA-B in the PSORS1 locus [93]. Its location within the said psoriasis susceptibility locus and being highly polymorphic makes it a promising candidate gene. Especially a $(GCT)_n$ trinucleotide repeat in the transmembrane region of MICA has demonstrated replicated association with psoriasis.

A number of four, five, six or nine GCT copies are designated as microsatellite alleles MICA-A4, -A5, -A6 and -A9. Similarly, the $(GCT)_4(GGCT)$ variant is referred to as MICA-A5.1. In total, nine case-control studies on the associations of those MICA alleles with psoriasis have been identified. While Grubic et al 2004 [160] studied exclusively A4, A5 and A6 alleles, the other studies tested all repeats mentioned above (Table 4.11). As the MICA-A9 variant showed the highest number of positive reports, a meta-analysis was performed.

Studies excluded from the meta-analysis of MICA-A9. Two studies investigated the presence of the (GCT)n triplet repeat in normal populations. Bolognesi et al 2001 [42] described frequencies of MICA microsatellite alleles in a random Italian panel (n = 101). They were highest for the A5.1 allele (31.6%) and lowest for A5 and A9 (13.6%). In contrast, the study by Pyo et al 2003 [378] found frequencies to be highest for A5 alleles (31.9%) and lowest for A5.1 alleles (10.8%) in healthy Koreans. This is indicative of different allele distributions in European and Asian countries.

Table 4.11.: Frequencies of MICA variants A4, A5, A5.1 and A6 in case-control studies on psoriasis

					Frequencies							
			Numbers		A4		A5		A5.1		A6	
Study [Ref]	**Country**	**Clin**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**
Choi 2000 [93]	Korea (A)	P	138	126	18.8	24.6	30.4	47.6	71.0	27.0	13.8	43.7
Cheng 2000 [89]	China (A)	P	300	200	9.8	15.0	25.7	39.0	41.5	23.0	5.0	9.7
Chang 2007 [77]	Taiwan (A)	PV	170	210	12.6	14.3	40.3	34.0	22.1	23.6	6.5	10.5
Chang 2003 [82]	Taiwan (A)	PV	105	160	12.4	13.4	42.4	34.4	18.6	23.1	8.1	11.2
Gonzalez 1999 [154]	Spain (E)	PV	45	177	20.0	23.7	22.2	23.1	57.5	51.4	37.7	46.8
Fojtikova 2009 [137]	Czech Rep (E)	PA	100	94	26.0	25.5	17.0	27.7	84.0	77.6	27.0	38.4
Chang 2007 [77]	Taiwan (A)	PA	102	210	16.7	14.3	38.2	34.0	28.9	23.6	2.5	10.5
Grubic 2004 [160]	Croatia (E)	PA	58	157	30.2	17.1	3.5	10.4	-	-	12.9	25.9
Gonzalez 2001 [151]	Israel	PA	52	73	9.6	15.0	13.4	31.5	40.3	46.5	48.0	54.7
Gonzalez 1999 [154]	Spain (E)	PA	65	177	20.0	23.7	13.8	23.1	40.0	51.4	43.0	46.8
Total			1135	1040	17.6	18.7	24.7	30.5	44.9	38.6	20.5	29.8

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Freq, frequencies of MICA microsatellite alleles A4, A5, A5.1 and A6 in %; Underlined allele frequencies differed significantly from controls;

Romphruk et al 2004 [403] and Korendowych et al 2006 [253] consider that MICA microsatellite alleles are carried by various alleles of extracellular domains. As a consequence, they analysed the association between those alleles and psoriasis. Korendowych et al 2006 [253] found that both MICA*002 and MICA*017 alleles possess nine GCT repeats in the transmembrane region and are therefore MICA-A9 alleles. While MICA*002 was significantly associated with psoriatic arthritis but not early-onset psoriasis without joint involvement, MICA*017 showed association with early-onset psoriasis but not psoriatic arthritis. In Romphruk et al 2004 [403] MICA*017 was increased in early-onset psoriasis as well, but did not reach statistical significance after correction (P = 0.0384, Pc = 0.8448). MICA*002, however, remained non-significant from the beginning.

Studies included in the meta-analysis of MICA-A9. The meta-analysis comprises nine case-control studies including eleven cohorts with 1253 cases and 1254 controls. For each study the leading author, year of publication, country, clinical variant of psoriasis, numbers and variant allele frequencies of patients and controls, mean age at onset (with standard deviation or range) and percentage of male patients are reported in Table 4.12.

The involved studies and their cohorts differ from each other in several points. For instance, they were carried out in a variety of different countries. There were three cohorts from Taiwan, one from China and one from Korea, yet all being of Asian ancestry. In addition, there were another five cohorts with European background, four from Spain and one from the Czech Republic. Only the study by Gonzalez et al 2001 [151] did not fit into this classification of Asian and European populations as it was conducted on Jewish subjects from Israel.

Moreover, the studies involved a number of different clinical psoriasis variants. Psoriasis vulgaris, the most common form, was investigated by four studies with Gonzalez et al 2000 [152] studying exclusively early-onset psoriasis vulgaris patients. Psoriatic arthritis was studied five times while two studies did not provide the underlying clinical phenotype and interestingly included high percentages of early-onset forms.

The studies by Choi et al 2000 [93] and Fojtikova et al 2009 [137] aimed to further investigate the influence of age at onset or rather the dependency on different onset types. To do so, they divided their samples into early-onset and late-onset cohorts and analysed them independently of each other in order to obtain a direct comparison.

Differences concerning age at enrollment and gender of patients were not eye-catching. Whenever provided, age ranges stretched between childhood and old age. Male/ female ratios were in balance in all but the two studies of Chang et al in 2003 and 2007 [82, 77]. This was due to the fact that preferentially male subjects were recruited from Taipei Veterans General Hospital.

Results of the meta-analysis of MICA-A9. The performed meta-analysis on all studies yielded a significant result (OR = 1.51, 95%CI = 1.10-2.08, P = 0.0113) by applying a random effects model (Figure 4.32). Odds ratios in the individual studies ranged from 0.74 to 3.57, reflecting the large between-study heterogeneity of 82.2% (inconsistency I^2) with Chochran Q test showing a highly significant result (P < 0.0001). No evidence

Table 4.12.: Characteristics of studies included in meta-analysis of MICA-A9 variant in psoriasis

			Numbers		Freq				
Study [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**Age**	**Onset**	**Male**
Choi 2000 [93]	Korea (A)	P (72%)	138	126	29.7	28.6	(12-83)	$\leq 40 \leq$	52.2
Cheng 2000 [89]	China (A)	P (84%)	300	200	18.0	13.3	(8-72)	$\leq 40 \leq$	59.7
Chang 2007 [77] $^{\Phi 1 \Psi 1}$	Taiwan (A)	PV (49%)	170	210	18.5	17.6	52.1 (7-84)	$\leq 40 \leq$	72.4
Chang 2003 [82] $^{\Psi 1}$	Taiwan (A)	PV (53%)	105	160	18.6	17.8	57.7 (11-84)	$\leq 40 \leq$	75.2
Gonzalez 2000 [152]	Spain (E)	PV1	95	104	30.5	30.7	-	26.9 (15.1)	41.1
Gonzalez 1999 [154] $^{\Phi 2}$	Spain (E)	PV	45	177	31.1	29.9	31 (10.5)	-	55.6
Fojtikova 2009 [137]	CR (E)	PA (67%)	100	94	46.0	30.8	54.6	$\leq 40 \leq$	49.0
Chang 2007 [77] $^{\Phi 1}$	Taiwan (A)	PA (74%)	102	210	13.7	17.6	45.6 (19-79)	$\leq 40 \leq$	52.0
Gonzalez 2002 [153] $^{\Psi 2}$	Spain (E)	PA	81	110	60.0	30.0	48 (13)	31 (11)	60.5
Gonzalez 2001 [151]	Israel	PA	52	73	55.7	27.3	-	36.4 (15.7)	-
Gonzalez 1999 [154] $^{\Phi 2 \Psi 2}$	Spain (E)	PA	65	177	58.4	29.9	46 (12.5)	29 (11.5)	56.9
Total			1253	1254	34.6	25.1			

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Freq, frequency of the MICA microsatellite allele A9 in %; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Age, mean age of patients with standard deviation or rage in brackets; Onset, mean age at onset with standard deviation or range in brackets; $\leq 40 \leq$, patients with onset before and after 40 years (early- and late-onset psoriasis) involved; Male, percentage of male patients in %; CR, Czech Republic; P, psoriasis without further specification; PV, psoriasis vulgaris; PV1, early-onset psoriasis vulgaris (Type 1); PA, psoriatic arthritis; $^{\Phi 1-2}$, these studies use the same control subjects, respectively; $^{\Psi 1-2}$, these studies may show an overlap of study populations, respectively; - , data not provided in the article;

of publication bias was found by Egger's regression test (P = 0.6672) nor by funnel plot analysis (Figure 4.33).

The study of Gonzalez et al 2002 [16] which investigated cases suffering from psoriatic arthritis achieved the highest association estimate indicating a particularly strong association. After stratification by the presence of joint involvement, analysis indicated that the MICA A9 allele was significantly associated with psoriatic arthritis only (OR = 2.24, 95%CI = 1.27-3.93, P = 0.005) (Figure 4.34b). Between-study heterogeneity remained significant and there were still no signs of publication bias (Figure 4.35b).

Apart from psoriatic arthritis, the original study by Cheng et al 2000 [89] without specified clinical subtype showed a borderline significant association with psoriasis, while the other unspecified psoriasis sample and all psoriasis vulgaris sample did not show significance (Figures 4.34a and 4.35a). These facts speak for a psoriatic arthritis specific association.

In addition, a putative influence of disease onset or rather onset type was assessed. There was a borderline significant association of the mainly early-onset cohort (84%) of Cheng et al 2000 [89]. In contrast, the early-onset cohort of Gonzalez et al 2000 [152] did not reach a significant association estimate. As mentioned, Choi et al 2000 [93] and Fojtikova et al 2009 [137] carried out a direct comparison between early-onset and late-onset psoriasis subgroups. Both achieved a higher odds ratio for late-onset psoriasis.

Table 4.13.: Association of MICA-A9 with psoriasis according to onset type

				Association		
Study [Ref]	**Type**	**Number**	**Frequency**	**OR**	**95%CI**	**P value**
Fojtikova 2009 [137]	P1	67	40.3	1.51	0.93-2.47	9.65E-02
	P2	29	58.6	3.18	1.66-6.11	1.81E-04
	P1+P2	100	460.7	1.91	1.23-2.96	2.49E-03
Choi 2000 [93]	P1	99	28.3	0.99	0.64-1.52	1.00E+00
	P2	39	33.3	1.25	0.69-2.22	4.79E-01
	P1+P2	138	29.7	1.06	0.71-1.57	8.48E-01

Study, studies given by first author and year of publication; Ref, reference number; Type, onset type of psoriasis; P1, early-onset psoriasis (Type 1); P2, late-onset psoriasis (Type 2); Numbers, numbers of patients and controls; P, patients; C, controls; Frequency, frequency of the MICA-A9 allele given in %; OR, odds ratio, 95%CI, confidence interval; P value, calculated by Fisher's exact test;

The early-onset group of Fojtikova et al lost significance compared to the analysis of all psoriasis subjects (Table 4.13).

Dependency on ethnic origin might be a possible reason for the lack of association in the psoriatic arthritis cohort of Chang et al 2007 [77]. It is the only non-significant sample and at the same time the only sample from an Asian country in the psoriatic arthritis group. This indicates a population specific pattern of inheritance as associations were significant for Czech, Spanish and Israeli samples. Still, more studies on Asian psoriatic arthritis subjects are needed to validate this hypothesis. Especially as the high percentage of early-onset subjects in the Asian study could explain the lack of association as well.

The mean frequency of the MICA A9 allele was 25.1% among all normal controls, Chinese showing a lower prevalence than the other populations. In detail, frequencies of the MICA A9 allele in Europeans, Israeli, Koreans and Chinese were 30.4%, 27.3%, 28.6% and 16.2%, respectively. Interestingly different Asian populations showed significantly deviating frequencies (Table 4.12).

Discussion of the meta-analysis of MICA-A9. The present meta-analysis promoted a contribution of MICA-A9, representing nine copies of GCT, to psoriasis susceptibility. Yet the association was mainly limited to psoriatic arthritis. Four out of five psoriatic arthritis cohorts showed significant results, three even indicating a more than 3-fold risk. In addition to that, the association seemed not to be only phenotype specific but also population specific. The non-significant psoriatic arthritis study was performed on individuals from Taiwan, while the others involved Czech, Spanish and Israeli subjects.

Another explanation for the lack of association in the said study could be the high percentage of early-onset psoriasis patients. Direct comparisons of early- and late-onset subgroups had shown higher estimates for the latter, while a borderline significant association of a mainly early-onset psoriasis cohort holds against this hypothesis. Yet the

undefined clinical subtype of this cohort might cause bias. Two excluded case-control studies showed conflicting results on this matter [403, 253]. Hence, additional data will be needed to rule out a dependency on age at onset and/or ethnicity. Gender or age at enrollment did not seem to have an influence on the association.

Interestingly, the A9 allele was rarer in Chinese control individuals than in Europeans, Israeli and Koreans. In general, A9 was less frequent than A5, A5.1 and A6 and more frequent than A4 in all controls subjects. While MICA-A5.1 showed the highest population-based frequency (38.6%) in Europe, mainly A5 was observed in Asian populations. These differing allele distributions in European and Asian countries were confirmed by two excluded studies on healthy populations [42, 378].

In addition to the results of association studies, MICA is supported as a candidate gene by functional aspects. For example, a specialized role in the immune response as a second lineage of major histocompatibility complex antigens was suggested [155]. Furthermore, the tissue expression pattern promotes it as a risk factor for spondylarthropathies in general and for psoriatic arthritis in particular which seems independent of HLA-Cw*0602 [154].

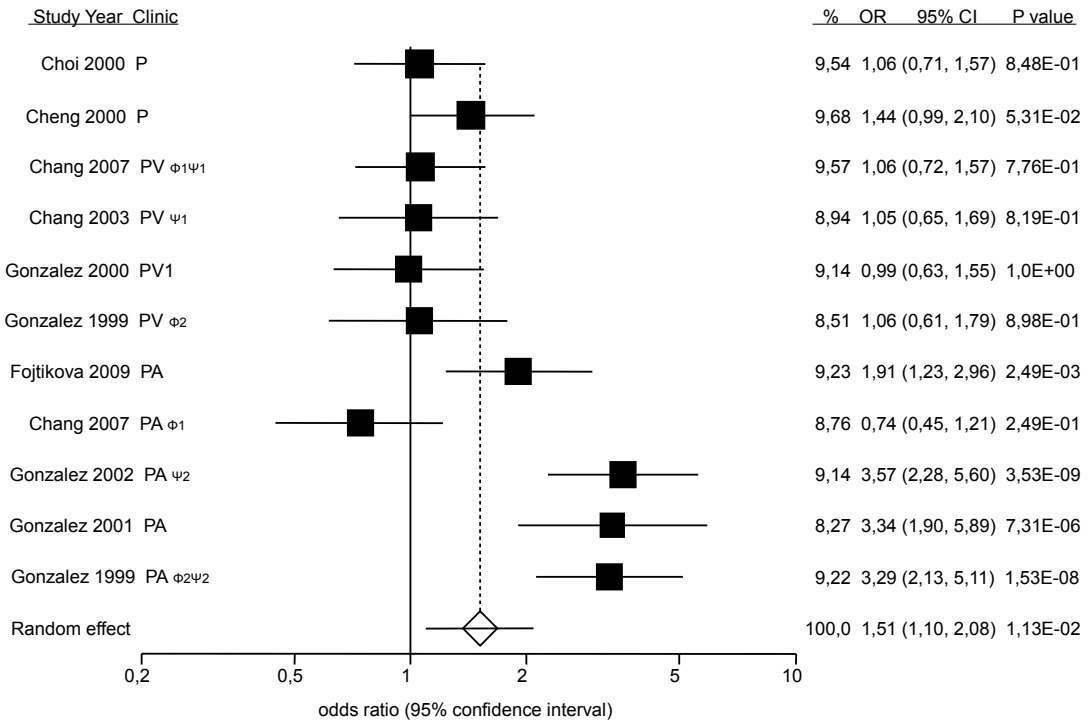


Figure 4.32.: Association of MICA-A9 with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.12.

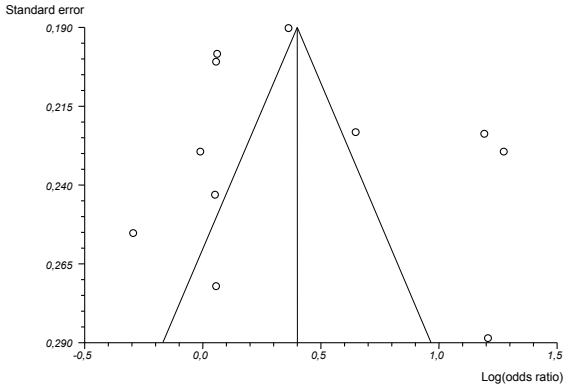
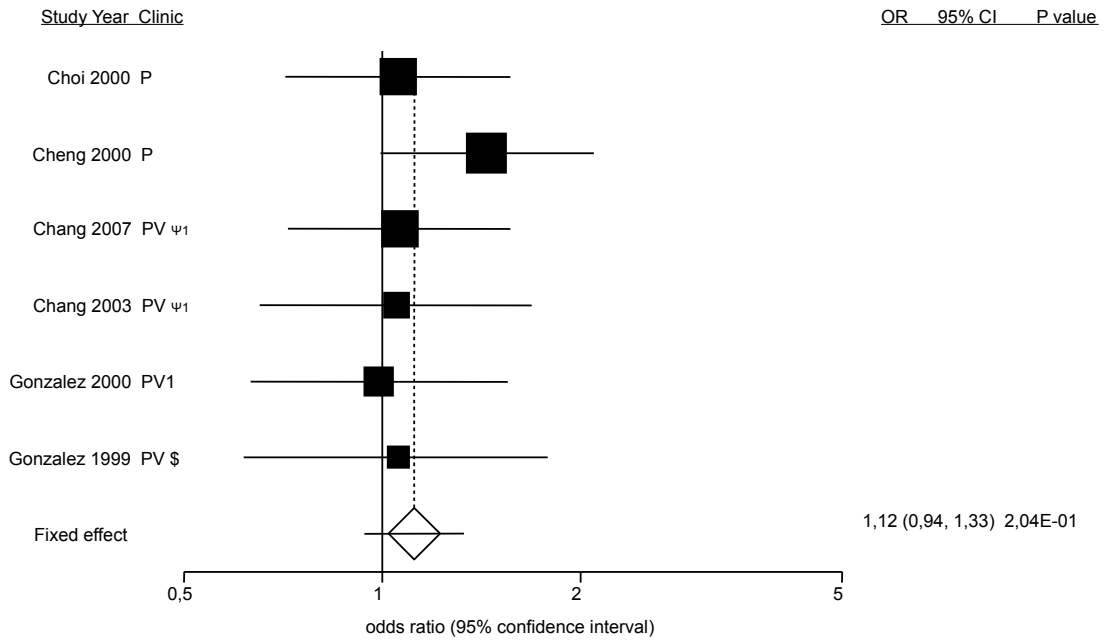
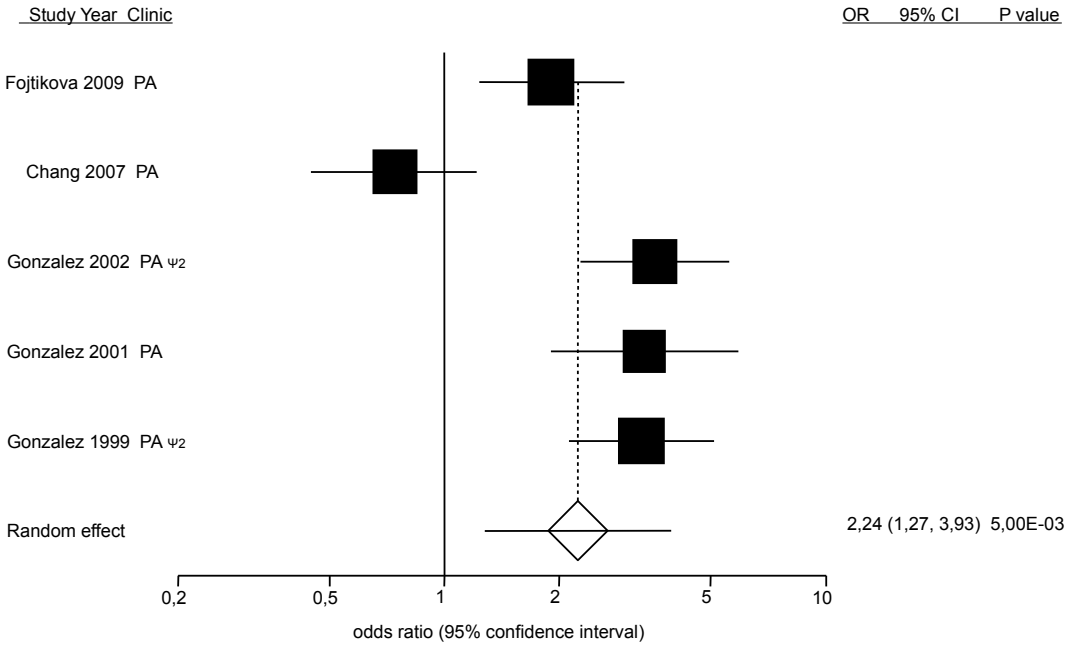


Figure 4.33.: Funnel plot showing log(OR)s and standard errors for the association of MICA-A9 with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.6672.

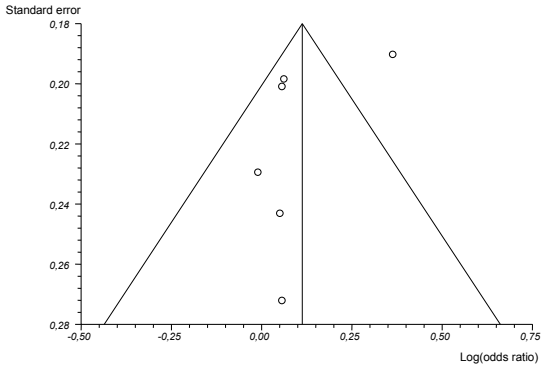


(a) Psoriasis without joint involvement

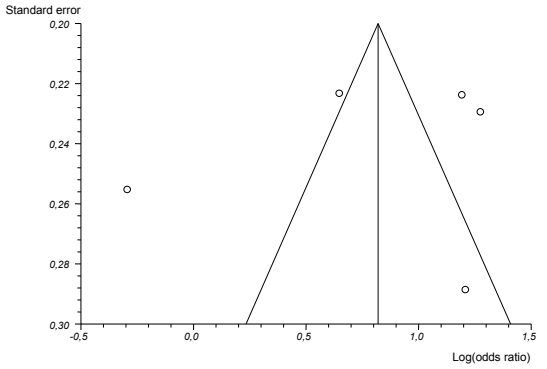


(b) Psoriatic arthritis

Figure 4.34.: Association of MICA-A9 with (a) psoriasis without joint involvement and (b) psoriatic arthritis. Forest plots showing ORs and 95% CIs for the studies (given by first author, year and country) included in the meta-analyses. Abbreviations see Table 4.12.



(a) Psoriasis without joint involvement



(b) Psoriatic arthritis

Figure 4.35.: Funnel plots showing log(OR)s and standard errors for the association of MICA-A9 with psoriasis in (a) psoriasis without joint involvement and (b) psoriatic arthritis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P values >0.05; (a) P = 0.2865; (b) P = 0.7865.

4.2.12. CDSN variants +1243C/+619T and haplotypes *5/*TTC

The CDSN gene (S gene) lies in the MHC class I region approximately 160 bp telomeric to HLA-C [143]. It encodes corneodesmosin which is found in the epidermal layer and is believed to play an important role in desquamation. As CDSN forms part of PSORS1 on chromosome 6p21.3, it was proposed as a candidate gene for psoriasis.

The initial *PubMed* search identified a large number of articles on the relation between CDSN variants and psoriasis. Not all of these variants showed positive reports (Table B.2, p. 243). For six single nucleotide polymorphisms, however, there was evidence of association in at least one published study: +619T, +722T, +971T, +1215G, +1236T and +1243T (Table B.1, p. 235).

Of these variants, +619T and +1243C were best investigated by far. A total of 16 studies dealt with the former and 21 with the latter. In addition, they form the so called CDSN*5 allele together with +1240G and the CDSN*TTC haplotype together with +1236T. The number of investigations was sufficient to perform meta-analyses on CDSN*5, CDSN*TTC and their constituent SNPs +1243C and +619T.

Table 4.14.: Characteristics of family studies on CDSN variants (+1243C, +619T) and haplotypes (CDSN*5, CDSN*TTC) in psoriasis

				Association			
Study [Ref]	**Country**	**Clinic**	**Families**	**+1243C**	**+619T**	***5**	***TTC**
Fan 2008 [130]	China	PVG	163	-	-	-	Yes
Nair 2006 [324]	Europe	PVAG	678	-	-	-	Yes
Ameen 2005 [8]	Japan	PV2	153	Yes	-	Yes	Yes
Asumalathi 2002 [19]	Europe, India	PV (mostly)	419	Yes	Yes	-	-
Schmitt-Egenolf 2001 [422]	Germany	PV1	52	Yes	-	-	Yes
Enerback 2000 [123]	Sweden	PV	232	Yes	Yes	-	-
Allen 1999 [7]	UK	P	152	Yes	No	Yes	-

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside; Families, number of families included; Association, stating if an association was detected or not; PV, psoriasis vulgaris; PV1, early-onset psoriasis vulgaris (Type 1); PV2, late-onset psoriasis vulgaris (Type 2); PVG, psoriasis vulgaris and guttate psoriasis; PVAG, psoriasis vulgaris, psoriatic arthritis and guttate psoriasis;

Meta-analysis of CDSN +1243C

The single nucleotide polymorphism +1243C is the best-studied genetic variant of CDSN. One of the first association studies was published by Tazi-Ahnini et al 1999 [472]. They found that the rare allele increased the risk of psoriasis as additional susceptibility factor independent from HLA-Cw6 with the effect being most pronounced in early-onset patients. The existence and strength of this effect shall be evaluated in the following meta-analysis.

Studies excluded from the +1243C meta-analysis. A sequence analysis by Jenisch et al 1999 [220] in 13 psoriasis multiplex families discovered 18 dimorphic sites in the

Table 4.15.: Characteristics of studies included in meta-analyses of CDSN variants +1243C and +619T in psoriasis

			Numbers		Frequencies +1243C		Frequencies +619T			
Author [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**P**	**C**	**Onset**	**Male**
Chang 2006 [76] $^{\Psi}$	Taiwan (A)	PV (52%)	178	203	79.2	71.4	65.7	68.5	$\leq 40 \leq$	70.2
Martinez-B 2005 [303]	Israel	PV1	59	79	67.8	62.0	79.6	81.0	27.4 (13.9)	66.1
Ameen 2005 [8]	Japan (A)	PV2	43	94	60.5	64.1	-	-	35	65.1
Allen 2005 [6] $^{\Phi 1}$	UK (E)	PV2	145	308	76.6	74.7	80.3	79.8	52.5 (40-81)	51.0
Romphruk 2003 [402]	Thailand (A)	PV (67%)	139	144	96.4	90.3	-	-	$\leq 40 \leq$	-
Chang 2003 [82] $^{\Psi}$	Taiwan (A)	PV (53%)	105	160	76.7	65.3	83.3	91.6	$\leq 40 \leq$	-
Veal 2002 [503]	India	PV	77	77	52.0	56.0	-	-	$\leq 40 \leq$	-
Orru 2002 [358]	Italy (E)	PV	147	120	59.9	60.0	94.5	95.5	31.7 (19.1)	57.1
Gonzalez 2000 [152] $^{\Phi 2}$	Spain (E)	PV1	95	104	96.8	86.5	97.8	97.1	26.9 (15.1)	41.1
Tazi-Ahnini 1999 [472]	UK (E)	PV	235	374	65.0	47.0	87.0	87.0	-	-
Ishihara 1996 [213]	Japan (A)	PV	63	88	79.4	88.6	81.0	84.1	-	-
Butt-1 2005 [57]	Canada (E)	PA	226	107	70.4	75.2	64.6	59.4	-	-
Butt-2 2005 [57]	Canada (E)	PA	210	99	64.5	69.4	63.7	67.8	-	-
Martinez-B 2003 [304] $^{\Phi 2}$	Spain (E)	PA1	74	104	97.3	86.5	94.5	97.1	23 (9)	-
Asumalahti 2003 [16] $^{\Phi 1}$	UK (E)	PG $^{\#1}$	134	309	75.0	47.0	84.0	80.0	17.5	45.0
Asumalahti 2003 [16] $^{\Phi 1}$	UK (E)	PPP $^{\#2}$	106	309	43.0	47.0	83.0	80.0	51	18.0
Total +1243C			2036	2266	73.7	68.4				
Total +619T			1777	1951			81.5	81.1		

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Freq, frequency of the CDSN +1243 C allele in % ; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Onset, mean age at onset with standard deviation or range in brackets; $\leq 40 \leq$, patients with onset before and after 40 years (early- and late-onset psoriasis) involved; Male, percentage of male patients in %; PV, psoriasis vulgaris; PV1, early-onset psoriasis vulgaris (Type 1); PV2, late-onset psoriasis vulgaris (Type 2); PA, psoriatic arthritis; PA1, early-onset psoriatic arthritis (Type 1); PG, guttate psoriasis; PPP, palmoplantar pustulosis; $^{\Phi 1-2}$, these studies use the same control subjects, respectively; $^{\Psi}$, these studies may show an overlap of study populations, respectively; $^{\#1}$, 56% guttate flare of PV; $^{\#2}$, 18% PPP and PV; - , data not provided in the article;

CDSN gene including +1243C. Two years later, Guerrin et al 2001 [161] replicated and extended this finding by analysing the CDSN sequence in 8 psoriatic patients and 6 controls. They ascertained a total of 26 dimorphic sites and found that the amino acid substitution caused by +1243C was able to modify CDSN phosphorylation sites [161].

In addition, there were five family-based analyses which concordantly reported significant associations of the CDSN +1243C variant with psoriasis. For each study first author, year of publication, clinical psoriasis variant, number of families and outcome are listed in Table 4.14.

A case-control study by Martinez-Borra et al 2003 [304] had to be excluded from the meta-analysis as it used the same psoriasis sample set as Gonzalez et al 2000 [152]. Consequently, only the latter was included in order to prevent bias. Yet Martinez-Borra et al 2003 [304] investigated an additional psoriatic arthritis cohort.

Studies included in the +1243C meta-analysis. A total of 14 case-control studies were included in the meta-analysis containing 16 cohorts with 1993 patients and 2172 healthy control subjects. Table 4.15 presents some characteristics of the studies and classifies them according to clinical psoriasis variants. Most studies analysed psoriasis vulgaris as this is the commonest psoriasis phenotype. In addition, there were three reports on psoriatic arthritis and two on rare psoriasis variants involving guttate psoriasis and palmoplantar pustulosis.

Concerning disease onset, an early-onset type and a late-onset type of psoriasis can be distinguished. Half of the studies provided information on the distribution of these onset types with three studies involving early-onset patients only and two studies involving late-onset only. As a different degree or pattern of inheritance is discussed for those types the composition of study groups is a potential source of variability.

Most studies gave no concrete statement on the age of the participants. Yet whenever a range was provided it reached from childhood to old age except from one cohort. Palmoplantar pustulosis cases of Asumalahti et al 2003 [16] comprised exclusively adults beyond the age of 30 years, which is not surprising as the mean age at disease onset was 51 years.

The majority of the studies were conducted on subjects form Europe or with European ancestry. All psoriatic arthritis cohorts and cohorts with rare phenotypes were Europeans, while the distribution of ethnicities was more balanced in the psoriasis vulgaris cohorts with nearly 50% from Asia. In addition, there was one sample from Israel and one from India.

Results of the +1243C meta-analysis. The overall meta-analysis supported an association between the CDSN +1243 C allele and psoriasis (OR = 1.37, 95%CI = 1.05-1.80, P = 0.0209). The corresponding forest plot in Figure 4.36 shows that individual odds ratios ranged between 0.78 and 5.60 with an outlier of 0.49. This between-study heterogeneity was found to be significant by Cochran Q test ($P < 0.0001$) and thus a random effects model was applied. Publication bias was not indicated by funnel plot analysis (Figure 4.37) nor by Egger's regression test (P = 0.9644).

Stratification by psoriasis subtype indicated that CDSN +1243C was significantly associated with psoriasis vulgaris (OR = 1.37, 95%CI = 1.06-1.78, P = 0.0166). In addition, the original case-control study by Asumalahti et al 2003 [16] showed a pronounced association with guttate psoriasis (OR = 3.39, 95%CI = 2.44-4,74, P = 5.92E-15). The association estimate was more than two times higher compared to psoriasis vulgaris. However, a very low mean age at onset (17.5 years) must be taken into account as well.

For psoriatic arthritis, only one out of three case-control studies had shown significant association (Figure 4.36). This single positive result by Martinez-Borra et al 2003 [304] might be explained by small sample size which can lead to an overestimation of the effect or dependency on onset type as they involved early-onset patients only.

Besides psoriatic arthritis, there was no evidence for association between CDSN +1243C and palmoplantar pustulosis either. The original report by Asumalahti et al 2003 [16] did not reach statistical significance. Yet the result might be influenced by a late-onset

type as the mean age at onset was very high (51 years) in this cohort.

In order to investigate a putative dependency on onset types, separate meta-analyses on early-onset and late-onset psoriasis were performed. Only psoriasis vulgaris samples were used for the stratification as the inclusion of different phenotype might have caused bias. There were two studies on early-onset only and two on late-onset only, while two studies investigated both onset types separately. The comparison of 339 early-onset psoriasis patients and 320 late-onset psoriasis patients indicated a significant association of CDSN +1243C polymorphism with early onset psoriasis only.

- Early-onset: OR = 2.51, 95%CI = 1.38-4.55, P = 0.0025; Figures 4.38a, 4.39a
- Late-onset: OR = 1.16, 95%CI = 0.93-1.43, P = 0.181; Figures 4.38b, 4.39b

Stratification according to ethnicity was performed exclusively on psoriasis vulgaris samples as well. This decision was based on the fact that meta-analyses of different psoriasis subtypes yielded deviating results. In addition, all subjects suffering from another phenotype than psoriasis vulgaris were exclusively from European origin. The meta-analyses revealed a significant effect in subjects from European origin, while significance was lost in Asian populations.

- Europe: OR = 1.64, 95%CI = 1.05-2.58, P = 0.0311; Figures 4.40a, 4.41a
- Asia: OR = 1.26, 95%CI = 0.79-2.02, P = 0.333; Figures 4.40b, 4.41b

Yet some confounding factors have to be considered. First, the distribution of onset types was not balanced with an early-onset cohort in the European analysis only. Second, the meta-analysis on Asian subjects contained an outlier in the opposite direction. When it was excluded, a significant outcome could be achieved for Asian populations as well.

The mean frequency of the CDSN +1243 C allele was 68.4% among all control populations, being highest in Asians (75.9%) and second highest in Europeans (67.1%). Controls from Israel showed slightly lower allele frequency of 62.0% and controls form India of 56.0%.

Discussion of the +1243C meta-analysis. The performed meta-analysis demonstrated a significant association of the CDSN +1243C variant with psoriasis, which is in conformity with the positive results of all family studies on the same topic. Concerning different ethnicities, the frequency of the +308 A allele varied substantially between ethnic groups, being highest in Asian and lowest in Indian control populations. Separate meta-analyses indicated a significant association with Europeans only. Excluding an outlier, however, a significant association could be confirmed for Asian populations as well. The two original studies on Israeli and Indian subjects, in contrast, showed negative results.

Stratification by psoriasis subtypes implied that the association was dependent on phenotypes. A significant relation to psoriasis vulgaris was validated by a meta-analysis

of ten case-control studies and by positive reports of family studies, while guttate psoriasis was strongly associated in a single study. In contrast, there was a single negative report for palmoplantar pustulosis and two negative reports against one positive report for psoriatic arthritis.

Stratification by onset type indicated an association with early-onset rather than late-onset psoriasis. Especially deviating results in the direct comparison of two studies supported this suspicion. In addition, a psoriatic arthritis sample and the guttate psoriasis sample with low mean ages at onset achieved high odds ratios as well, while the palmoplantar pustulosis sample with a very high mean age at onset yielded no significant result. Yet those observations might be confounded by psoriasis subtypes.

In conclusion, the present meta-analysis mainly indicated a correlation between CDSN +1243 C allele and early-onset psoriasis vulgaris in European populations, while data on different phenotypes and ethnicities was insufficient and/or conflicting. Yet CDSN haplotypes or other disease-associated polymorphisms of the CDSN gene or nearby genes in the MHC may contribute to disease susceptibility instead.

Therefore, other research protocols were used to further investigate CDSN as a putative genetic risk factor. An expression analysis, for example, indicated an increased expression of corneodesmosin in lesional psoriatic skin compared to non-lesional and normal skin. This significantly altered expression was observed in both the stratum spinosum and stratum corneum. Interestingly, there was no stratum spinosum immunoreactivity in other inflammatory skin disorders including chronic atopic dermatitis. [5]

Another functional analysis investigated the processing of the CDSN gene product. They found an altered proteolytic cleavage of corneodesmosin in lesional psoriatic skin leading to an impaired desquamation, a common feature of psoriasis. However, the proteolysis did not seem to be modified by single nucleotide polymorphisms of the CDSN gene. [433]

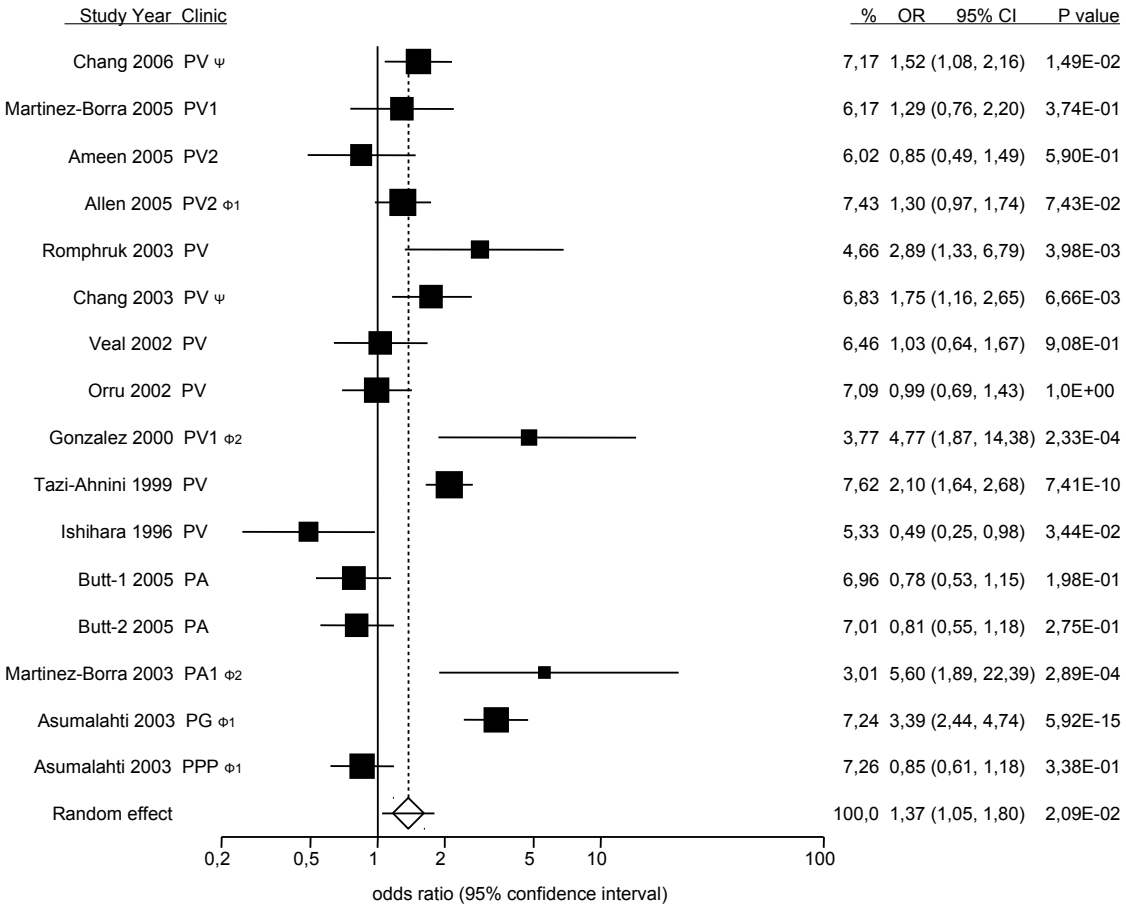


Figure 4.36.: Association of CDSN +1243 C allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.15.

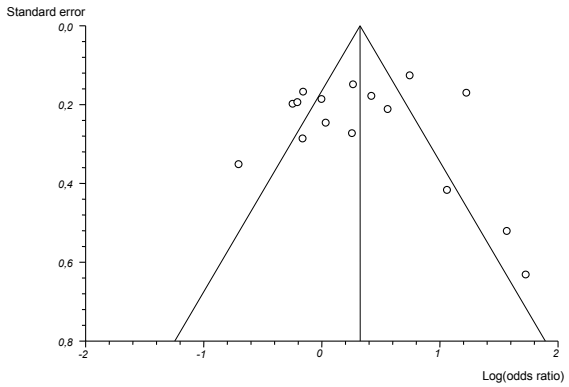
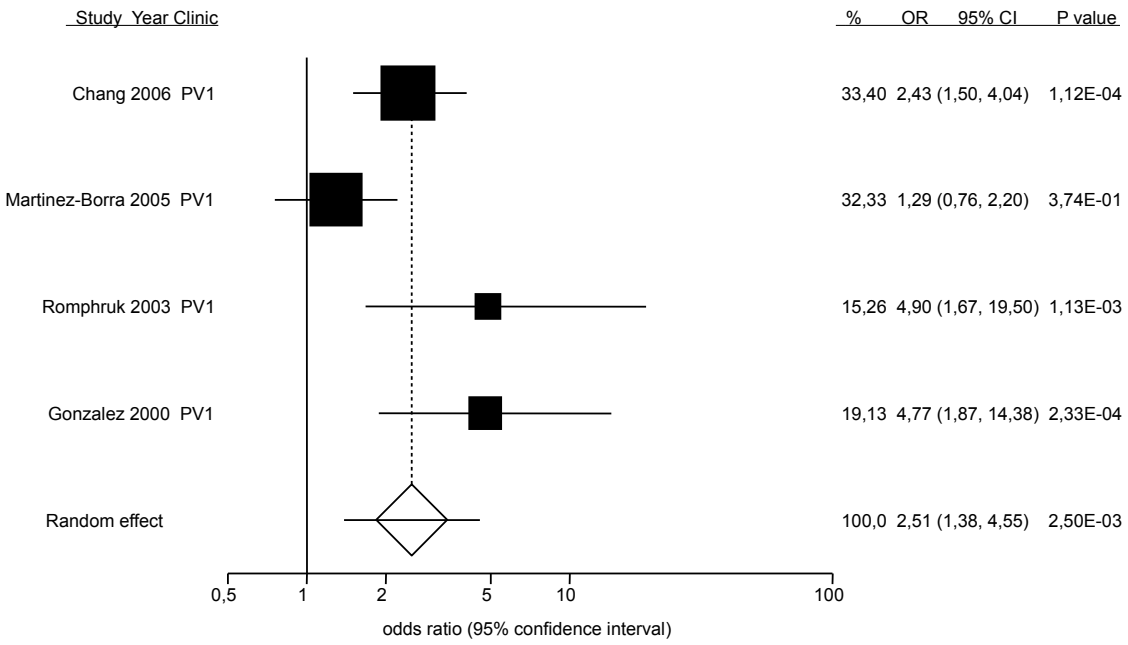
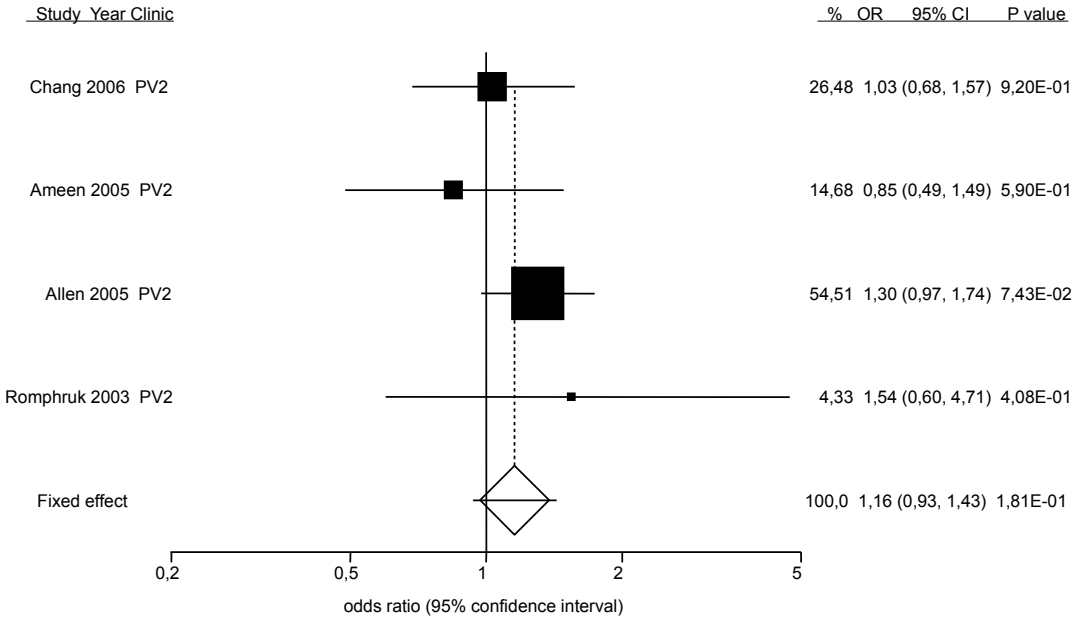


Figure 4.37.: Funnel plot showing log(OR)s and standard errors for the association of CDSN +1243 C allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.9644.

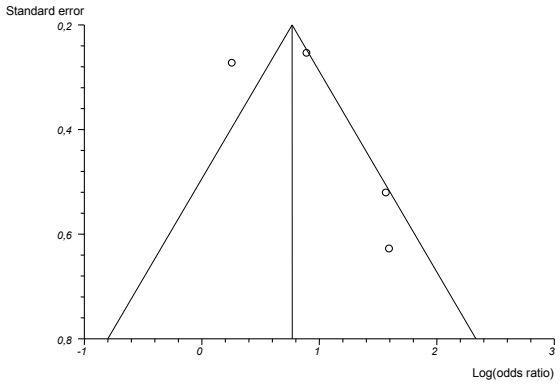


(a) Early-onset

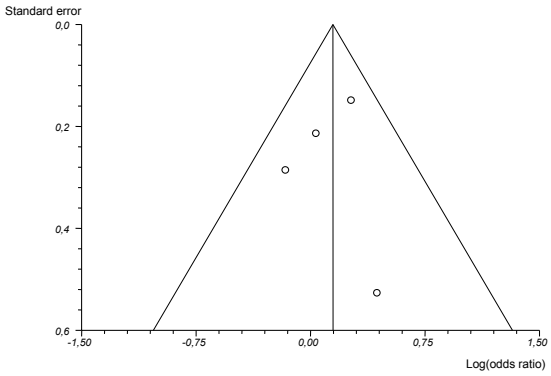


(b) Late-onset

Figure 4.38.: Association of CDSN +1243 C allele with (a) early-onset and (b) late-onset psoriasis. Forest plots showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analyses. %, weight; abbreviations see Table 4.15.

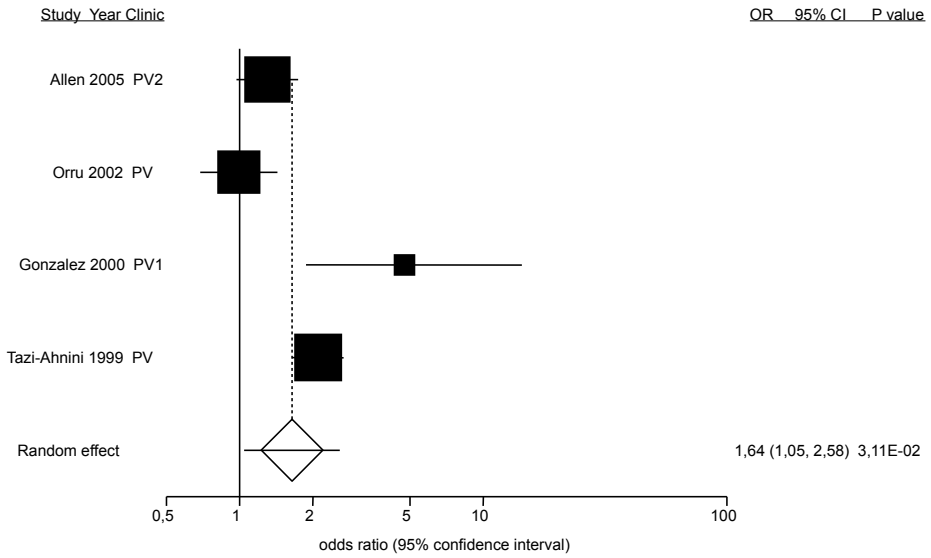


(a) Early-onset

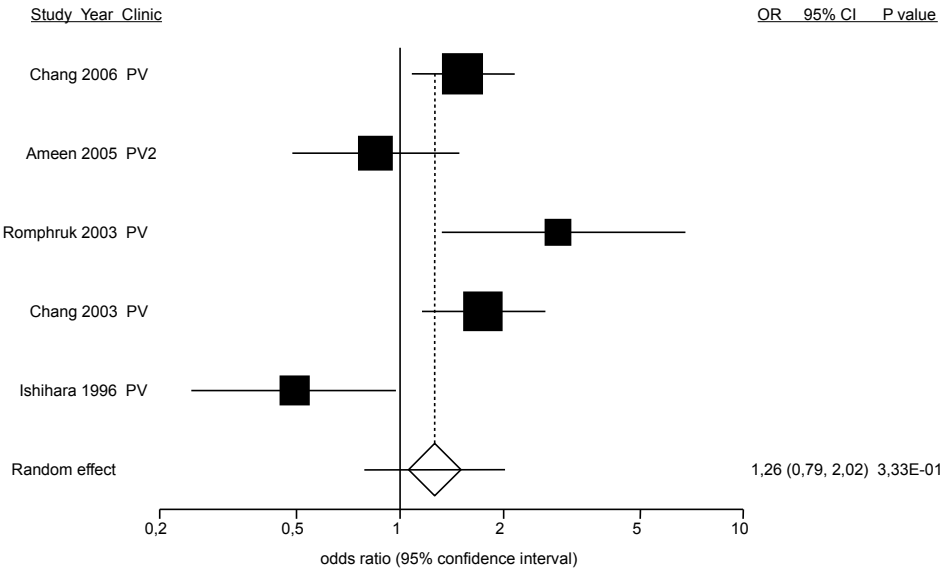


(b) Late-onset

Figure 4.39.: Funnel plots showing log(OR)s and standard errors for the association of CDSN +1243 C allele with (a) early-onset and (b) late-onset psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P values > 0.05; (a) P = 0.267; (b) P = 0.7536.

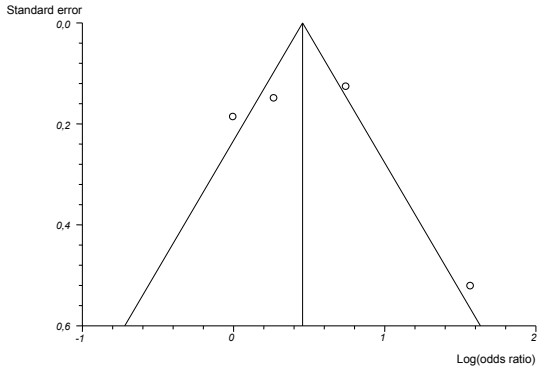


(a) Europe

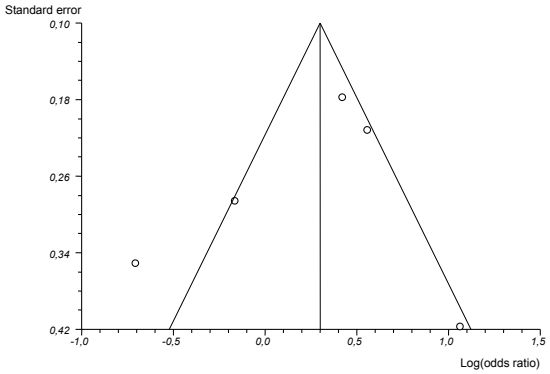


(b) Asia

Figure 4.40.: Association of CDSN +1243 C allele with psoriasis in (a) European and (b) Asian populations. Forest plots showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analyses. %, weight; abbreviations see Table 4.15.



(a) Europe



(b) Asia

Figure 4.41.: Funnel plots showing log(OR)s and standard errors for the association of CDSN +1243 C allele with psoriasis in (a) European and (b) Asian populations. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P values > 0.05; (a) P = 0.8133; (b) P = 0.6288.

Meta-analysis of CDSN +619T

A large proportion of the studies on the association between CDSN variant +1243C and psoriasis did an analysis of the +619T variant as well. Only the case-control studies of Veal et al 2002 [503], Romphruk et al 2003 [402] and Ameen et al 2005 [8] left out the additional polymorphism.

Studies excluded from the +619T meta-analysis. A sequence analysis by Jenisch et al 1999 [220] did not only discover +1243C but also +619T as a dimorphic site in the CDSN gene. The investigation by Guerrin et al 2001 [161] two years later, replicated this finding and found that the amino acid substitution caused by +619T was able to modify CDSN phosphorylation sites like the amino acid substitution caused by +1243C [161].

Three family studies were not only conducted on +1243C but also on +619T. First author, year of publication, clinical psoriasis variant, number of families and outcome are listed in Table 4.14 on page 129. The results for +619T were not as consistent, however, showing two positive and one negative report.

Similar to +1243C, a case-control study by Martinez-Borra et al 2003 [304] had to be excluded from the meta-analysis as it used the same psoriasis sample set as Gonzalez et al 2000 [152]. Consequently, only the latter was included in order to prevent bias. Yet Martinez-Borra et al 2003 [304] investigated an additional psoriatic arthritis cohort.

Studies included in the +619T meta-analysis. A total of 11 studies were included in the meta-analysis containing 13 cohorts with 1777 cases and 1951 controls. Table 4.15 on page 130 presents some characteristics of the studies and classifies them according to clinical psoriasis variants. Here, too, most studies analysed the common phenotype psoriasis vulgaris, three dealt with psoriatic arthritis and Asumalahti et al 2003 [16] investigated guttate psoriasis and palmoplantar pustulosis.

Concerning onset types, there were three early-onset cohorts and one late-onset cohort. Furthermore, the guttate psoriasis cohort showed a very low mean age at onset (17.5 years) whereas the palmoplantar pustulosis cohort showed a very high mean age at onset (51 years). These facts have to be taken into account as a different genetic contribution is discussed for different ages at onset.

Most studies gave no concrete statement on the age of the participants. Yet whenever a range was provided it reached from childhood to old age except from one cohort. Palmoplantar pustulosis cases of Asumalahti et al 2003 [16] comprised exclusively adults beyond the age of 30 years.

Relating to ethnicity, the majority of studies were conducted on subjects form Europe or with European ancestry. Especially all psoriatic arthritis cohorts and cohorts with rare phenotypes were Europeans. Additionally, there were three studies on Asian populations and Martinez-Borra et al 2005 [303] studied Jewish samples from Israel.

Results of the +619T meta-analysis. The performed meta-analysis on the association between CDSN +619T and psoriasis did not reach statistical significance (OR = 0.98,

95%CI = 0.86-1.11, P = 0.7701). Only one of the 13 reports had conceded a protective effect against psoriasis to the T allele. The forest plot in Figure 4.42 shows that individual odds ratios ranged from 0.46 to 1.38. As a low between-study heterogeneity was confirmed by Chochron Q test (P = 0.2689), a fixed effects model was applied. No publication bias was indicated by funnel plot analysis (Figure 4.43) nor by Egger's regression test (P = 0.301).

A separate analysis of psoriasis vulgaris did not yield significance either and data on different onset types was too limited to perform additional analyses. The only study reporting a significant outcome was performed on Taiwanese subjects implying a dependency on ethnicity. Still, further data on Asian samples was limited and two additional studies on Taiwanese and Japanese samples failed to replicate the finding.

The mean frequency of the CDSN +619 T allele was 81.1% among all normal controls and did not vary notably between different ethnicities (European: 83.0%, Asian: 83.0%, Israeli: 81.0%).

Discussion of the +619T meta-analysis. The performed meta-analyses did not support an associations of the CDSN +619T variant with psoriasis. The only study reporting a significant outcome was performed on Taiwanese subjects. Still, a genetic association dependent on ethnicity seems rather unlikely as two additional studies on Taiwanese and Japanese samples failed to replicate the finding. The prevalence of the +619 T allele was high in all ethnic groups showing a mean allele frequency of 81.1% in all control populations. Stratification by psoriasis phenotype did not lead to positive results either and data on different onset types was too limited.

In addition to the meta-analysis involving case-control studies, three family studies had shown conflicting results on the association of CDSN +619T as well. While two had reached statistical significance, the third lacked evidence of association.

Although eligible genetic data suggest that the CDSN +619T polymorphism is not related to psoriasis per se, a contribution to disease-associated haplotypes remains conceivable. For instance, it forms part of CDSN*5 together with +1243C and +1240G as well as CDSN*TTC together with +1243C and +1236T. Putative associations of these haplotypes with psoriasis will be discussed in the following subsections.

As mentioned, the present meta-analysis indicates the absence of a correlation between CDSN +619 allele and psoriasis. Yet between-study heterogeneity relating disease phenotype, onset type and ethnicity limits validity. Studies on Asian populations are needed to confirm or contradict an association to this ethnic group in particular. In addition, data on psoriatic arthritis and rare subtypes was limited. The functional relevance of CDSN polymorphisms was discussed earlier.

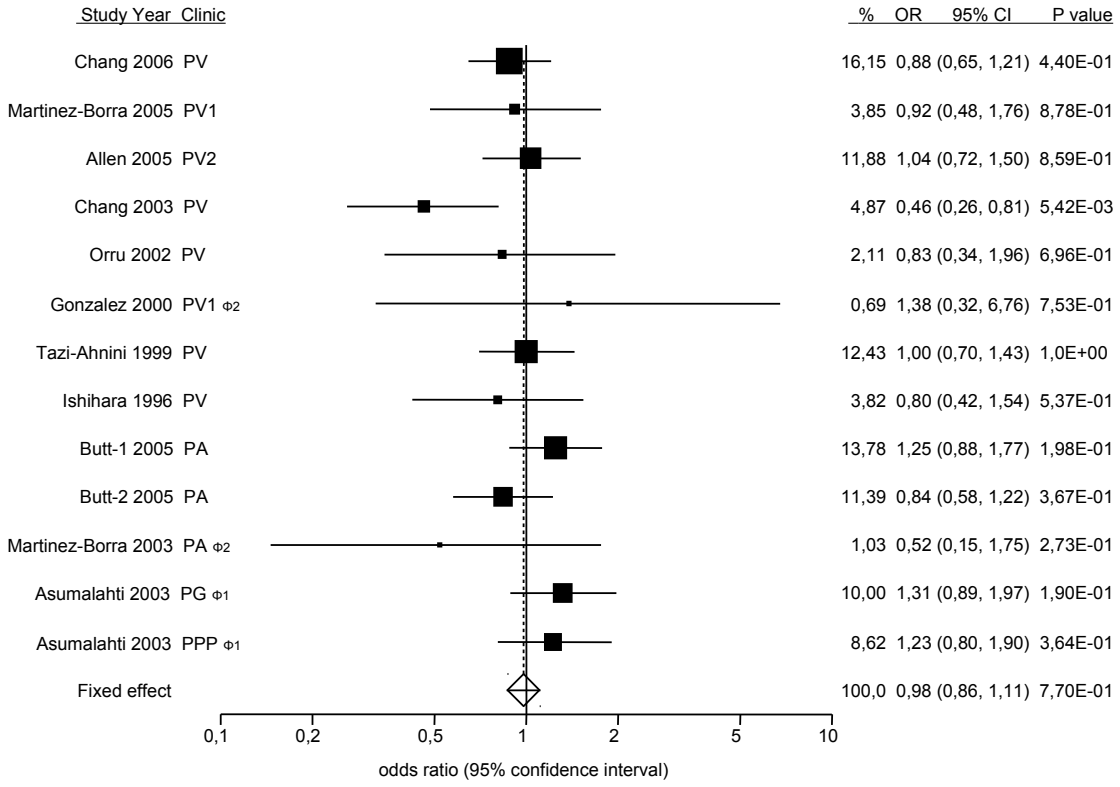


Figure 4.42.: Association of CDSN +619 T allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.15.

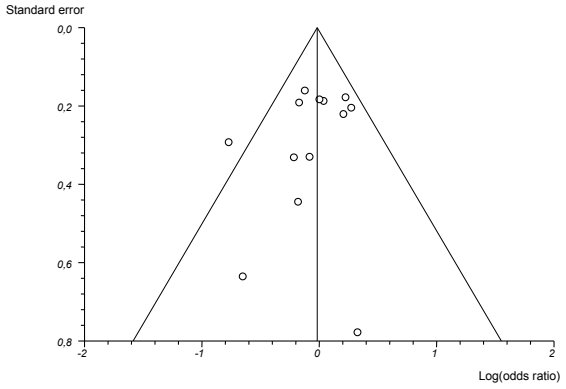


Figure 4.43.: Funnel plot showing log(OR)s and standard errors for the association of CDSN +619 T allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.301.

Meta-analysis of CDSN*5 haplotype

A number of studies did not only investigate the association of single variants with psoriasis, but also with the CDSN*5 haplotype consisting of +619T, +1240G and +1243C. A total of five articles on both the polymorphisms alone and the combined CDSN*5 allele were identified. One additional publication which reported exclusively on CDSN*5, defined the haplotype as +619T and +1243C.

Studies excluded from the CDSN*5 meta-analysis. Two family studies were conducted on CDSN*5 and both showed consistent associations with psoriasis. First author, year of publication, clinical psoriasis variant, number of families and outcome are listed in Table 4.14 on page 129.

Studies included in the CDSN*5 meta-analysis. A total of six case-control studies were included in the meta-analysis, containing seven cohorts with 703 cases and 1508 control subjects. Characteristics of all but one study can be found in Table 4.15 on page 130. The additional study by Asumalahti et al 2000 [17] genotyped 100 Finnish psoriasis patients and 100 unaffected family members as controls. Most subjects suffered from psoriasis vulgaris but there were patients with guttate psoriasis or inverse psoriasis as well. Age at onset ranged form 3 to 80 years and male/female ratio was in balance.

Regarding all case-control studies, there were four psoriasis vulgaris samples, one guttate psoriasis sample and one sample with mixed phenotypes. Concerning disease onset, two studies contained late-onset subjects only and one study analysed onset types separately. In addition, mean age at onset was rather low in guttate psoriasis subjects (17.5 years). Neither mean age at onset nor exact distribution of onset types were provided in Tazi-Ahnini et al 1999 [472] and Asumalahti et al 2000 [17]. Information on onset types is important as a different mode of inheritance is discussed for early- and late-onset psoriasis.

Concerning different ethnicities, the spectrum is relatively small as nearly all studies were performed on subjects of European or Asian ancestry. In detail, there were three European samples as well as three Asian samples. Alone Martinez-Borra et al 2005 [303] studied Jewish samples from Israel. Most studies gave no concrete statement on the age of participants at enrollment, but whenever provided it ranged from childhood to old age.

Results of the CDSN*5 meta-analysis. The overall meta-analysis demonstrated an association between the CDSN*5 allele and psoriasis (OR = 2.24, 95%CI = 1.15-4.36, P = 0.0183). Odds ratios ranged from 0.99 to 14.51 showing a very high between-study heterogeneity confirmed by Cochran Q test (P < 0.0001). Thus meta-analysis was performed using a random effects model (Figure 4.44). No signs for publication bias were detected by funnel plot analysis (Figure 4.45) nor by Egger's regression test (P = 0.3691).

When looking at psoriasis subtypes, the highest association estimate was achieved for the guttate psoriasis sample (OR = 14.51, 95%CI = 8.68-25.51, P = 4.42E-41). Still,

this pronounced association might equally be phenotype dependent or onset dependent as the mean age at onset was very low in this sample. A direct comparison by Chang et al 2006 [76] favors the hypothesis of a onset dependent association, because the early-onset subset reached a significant results while the late-onset subset did not. In total, only one out of three late-onset cohorts showed a significant result (Figure 4.44).

Due to limited data, no further investigations on a possible dependency on phenotype or ethnicity were possible. The mean frequency of the CDSN*5 allele was 59.9% among all control populations varying substantially between 40.0% in Taiwanese and 85% in Finish.

Discussion of the CDSN*5 meta-analysis. The present meta-analysis showed a significant genetic association between the CDSN*5 haplotype and psoriasis, which is conformity with the positive reports of two family studies. The relation seemed to depend on age at onset as a direct comparison yielded significance for early-onset psoriasis only. In addition, two out of three late-onset samples failed to report a significant association. It remains unclear, however, if the strong correlation with the guttate psoriasis cohort of Asumalahti et al 2003 [16] depended on psoriasis phenotype or low mean age at onset.

Due to limited data, no further statement on a possible dependency on phenotype or ethnicity can be given. In summary, the present meta-analysis indicates a correlation

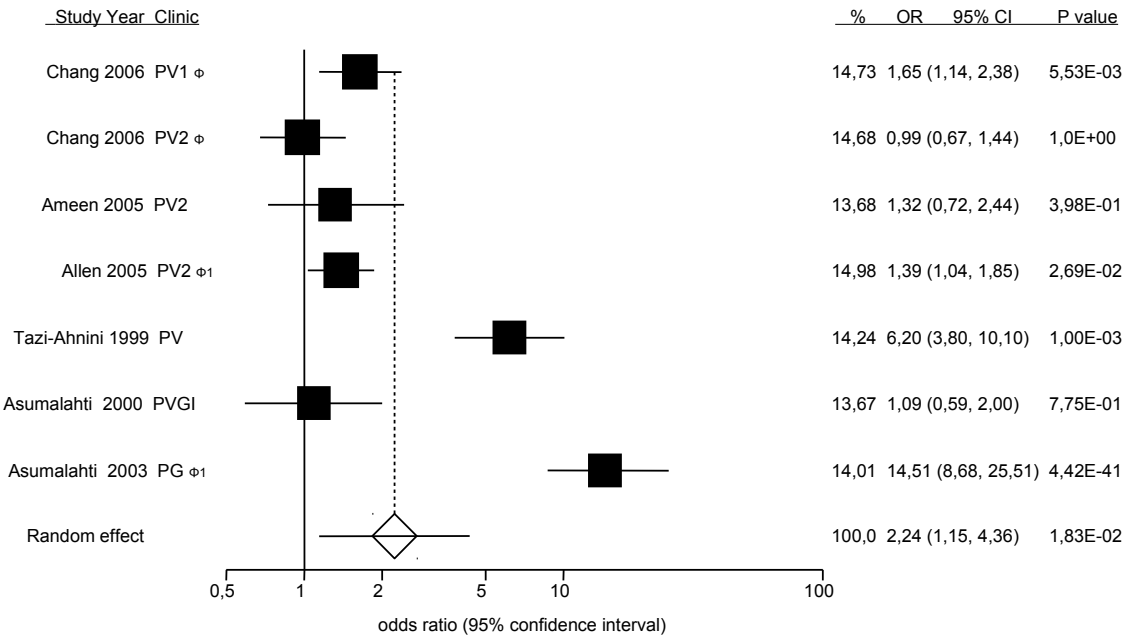


Figure 4.44.: Association of CDSN*5 haplotype with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.15.

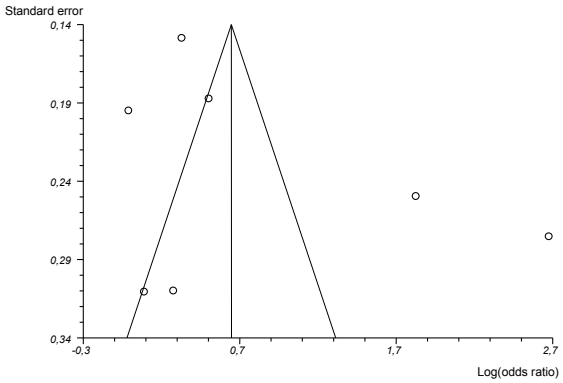


Figure 4.45.: Funnel plot showing log(OR)s and standard errors for the association of CDSN*5 haplotype with psoriasis. Bias indicators showed a significant deviation from the symmetry assumption, thus indicating publication bias: Egger's regression test P = 0.3691.

between the CDSN*5 haplotype consisting of +619T, +1240G and +1243C and psoriasis, but it is possible that +1243C alone accounts for the positive result.

While the meta-analysis of +1243C showed a highly significant result for this polymorphism alone, the meta-analysis of +619T suggested an absence of association. In addition, all association studies on +1240G and psoriasis did not reach statistical significance [76, 304, 304, 82, 152, 213] (Table B.2, p. 243).

Meta-analysis of CDSN*TTC haplotype

Fewer studies investigated the potential association of the CDSN*TTC haplotype consisting of +619T, +1236T and +1243C and psoriasis. A total of three publications containing four case-control sets on both the polymorphisms alone and the combined CDSN*TTC haplotype were identified. One additional publication involving two sample sets investigated the haplotype only.

Studies excluded from the CDSN*TTC meta-analysis. In addition to case-control data, four family studies were published on the association of CDSN*TTC with psoriasis. They tested psoriasis vulgaris, mixed phenotypes, early- and late-onset psoriasis with all of them showing positive results. For each study first author, year of publication, clinical psoriasis variant and number of families was listed in Table 4.14 on page 129.

Studies included in the CDSN*TTC meta-analysis. As none of the case-control studies had to be excluded, four studies containing 6 cohorts with a total of 572 cases and 620 healthy control subjects were included in the meta-analysis. Characteristics of all but one study can be found in Table 4.15 on page 130. The additional study by Chang et al 2007 [78] investigated 91 early-onset psoriasis patients, 83 late-onset psoriasis patients and 178 control subjects. All of them were Chinese and the patients

suffered from psoriasis vulgaris. The age of the patients ranged from 11 to 87 years (mean age = 55.4 years) and they were predominantly male.

Concerning clinical psoriasis variants, the composition was uniform as all studies involved psoriasis vulgaris. The two studies of Chang el al 2003 [78] and 2006 [76] analysed early- and late-onset subjects separately while Martinez-Borra et al 2005 [303] studied early-onset subjects only. Only Orru el al 2002 [358] did not classify the patients according to their age at onset. Still, the mean age at onset was rather low (31.7 years) similar to the early-onset cohort (27.4 years) of Martinez-Borra et al 2005 [303].

Relating to different ethnicities, the composition was rather mixed. Chang et al 2003 and 2006 [78, 76] studied Asian samples from China while Orru et al 2002 [358] involved Italian subjects with European ancestry. In addition, Martinez-Borra et al 2005 [303] studied Jewish samples from Israel. The age of participants ranged from childhood to old age and there was a higher percentage of male patients in all studies.

Results of the CDSN*TTC meta-analysis. The performed meta-analysis showed an association between the CDSN*TTC haplotype and psoriasis (OR = 1.87, 95%CI = 1.29-2.72, P = 0.001). Odds ratios ranged from 1.27 to 3.92 showing low between-study heterogeneity confirmed by Cochran Q test (P = 0.0003). Thus meta-analysis was performed using a fixed effects model (Figure 4.46). A borderline significant publication bias was found by Egger's regression test (P = 0.0509) (Figure 4.47).

The association estimates seemed to correlate with the age at onset. Both studies by Chang et al 2003 and 2006 [78, 76] reached significant values for the early-onset sample sets only. In addition, a sample with a rather low mean age at onset of 31.7 years by Orru et al 2002 [358] achieved the highest odds ratio with the highest significance. Only one negative result of an exclusively early-onset cohort of Martinez-Borra et al 2005 [303] stands against the hypothesis of a onset-dependent correlation.

Yet ethnicity might act as a putative confounder as the study was performed on Jewish subjects from Israel. The mean frequency of CDSN*TTC was 25.0% among all control populations, being lowest in Asians (20.0%) and highest in the Italians (30.6%).

Discussion of the CDSN*TTC meta-analysis. The present meta-analysis suggested a significant genetic association between the CDSN*TTC haplotype and psoriasis, which is conformity with the positive reports of four family studies. Here, too, the relation seemed to depend on onset types as two out of three early-onset samples reported a significant association while none of the two late-onset samples gave a positive report. It remains unclear, if the insignificant correlation in Martinez-Borra et al 2005 [303] comes from real lack of association with the early-onset sample or different ethnicity.

Although association data suggest that the CDSN*TTC haplotype is related to psoriasis, +1243C alone could account for the positive result. While the meta-analysis of +1243C showed a highly significant result for this polymorphism alone, the meta-analysis of +619T suggested an absence of association. In addition, all case-control studies on +1236T proposed that it was not associated with psoriasis [76, 303, 8, 57, 6, 358, 472] while only one family study reported a positive result [8].

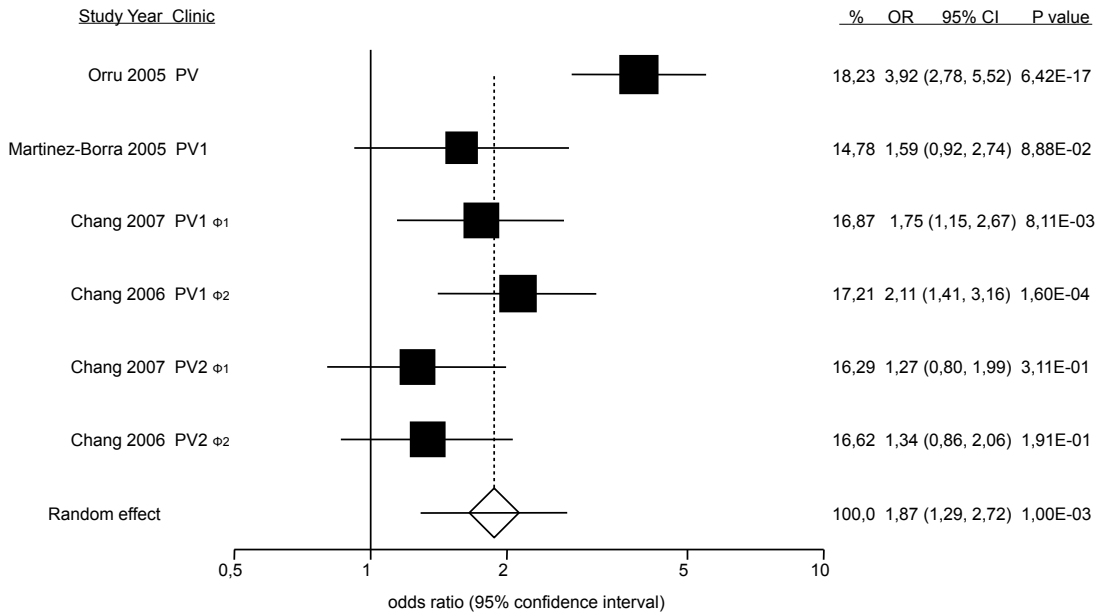


Figure 4.46.: Association of CDSN*TTC haplotype with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.15.

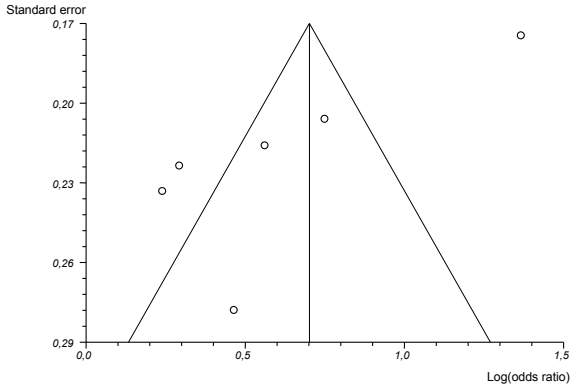


Figure 4.47.: Funnel plot showing log(OR)s and standard errors for the association of CDSN*TTC with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.0509.

4.2.13. TNF variants -308A, -238A and -857T

The TNF gene is another candidate lying in PSORS1 on chromosome 6p21.3. It encodes a proinflammatory cytokine which is involved in many biological processes including the pathogenesis of psoriasis [331]. The initial search identified a large number of association studies on TNF variants and psoriasis. Yet not all of the investigated polymorphisms showed positive reports (Table B.2, p. 243).

The three SNPs +308A, +238A and -857T, however, showed significant associations with psoriasis in more than one published study. Hereby, single nucleotide polymorphisms +308A and +238A were in the focus of interest, as in total 20 studies dealt with both of them and an additional three studies investigated +308A only. Still, there were at least six association studies involving eight cohorts on the TNF -857 T allele as well. As a consequence, three meta-analyses were performed.

Meta-analysis of TNF +308A

For the TNF +308 A allele, two meta-analyses already existed. Li et al 2007 [279] analysed ten psoriasis samples, six from Europe and four from Asia, while Rahman et al 2006 [385] investigated eight psoriatic arthritis cohorts from Europe and one from Japan.

Only the meta-analysis by Li et al confirmed an association between TNF +308A and European psoriasis samples, not reaching statistical significance for the Asian cohorts. Rahman et al was not able to support a relation between +308A and psoriatic arthritis. In order to provide a full picture on the associations with different clinical psoriasis variants and ethnicities, all samples of the discussed meta-analyses and nine new cohorts were merged into a new meta-analysis.

Studies excluded from the +308A meta-analysis. A sequence analysis by Nishibu et al 2002 [335] was carried out in order to identify polymorphisms the TNF gene. Of 37 Japanese patients, only one male patient suffering from generalized pustular psoriasis carried the AA genotype while all others showed the GG genotype and none the GA genotype.

The only family-based analysis by Jacob et al 1999 [216] did not reveal any correlation between TNF +308A and psoriasis. The 83 German trios investigated by TDT did not show abnormalities in the transmission of the A allele from parents to their offspring with early-onset psoriasis.

A case-control study of Alenius et al 2004 [4] used microsatellite markers to investigate the TNF locus. Yet no association between psoriatic arthritis and said locus was found in 120 Swedish patients and 94 controls. Balding et al 2003 [24] sequenced DNA of 147 psoriatic arthritis patients and 389 control subjects in order to reveal associations with several single nucleotide polymorphisms. While no SNP showed significant correlation with the disease per se, TNF +308 showed association with joint erosions, progression of joint erosions and age at onset. Corresponding genotyping data or association estimates were missing, however.

Another case-control study by Arias et al 1997 [10] could not be included in the meta-analysis as the article was not publicly available. They had reported a negative result for the +308A variant and 99 Caucasian psoriasis patients (65% type 1). The analysis by Hamamoto et al 2000 [165] was excluded due to a different reason. The case-control data of 20 Japanese psoriatic arthritis patients and 87 healthy control subjects, did not reach a risk allele frequency of 1% for +308A. As the allele frequency was similarly low in patients and controls, no significant association was detected.

Studies included in the +308A meta-analysis. The remaining 23 case-control studies consisting of 27 cohorts with a total of 3617 patients and 2662 healthy subjects. Table 4.16 presents some characteristics of the studies and organizes them according to the investigated clinical psoriasis variant. Psoriasis vulgaris and psoriatic arthritis have been the best studied. In addition, four studies did not specify the exact psoriasis variant while three involved a mixture of different phenotypes, including rare forms like psoriatic erythroderma, guttate psoriasis and nummular psoriasis. Another cohort consisted of palmoplantar pustulosis patients only.

More than half of the studies provided information on the distribution of onset types. In most cases, the portion of early-onset psoriasis was higher than the portion of late-onset psoriasis. Four studies even included exclusively patients with an disease onset before the age of 40. Only Chang et al 2003 [82] and Chang et al 2007 [77] had a balanced early-onset/late-onset ratio and Settin et al 2009 [429] counted with a lower percentage of early-onset patients. A direct comparison between the two onset types was provided in five studies [329, 26, 288, 106, 395].

The majority of studies were conducted on subjects form Europe or from European origin. Nearly 80% of psoriatic arthritis cohorts and 60% of psoriasis vulgaris cohorts were Europeans. In addition, there were a number of publications on Asian populations providing 40% of psoriasis vulgaris cohorts and one psoriatic arthritis cohort. The remaining studies were carried out in Egypt, Brazil and Israel.

Two thirds of the studies gave a concrete statement on the age of participants. While there were no studies on children only, a lot of studies showed a mixed age distribution from childhood to old age. The remaining studies involved adults only or did not provide information on the age of participants. However, reports on both early- and late-onset psoriasis might show a mixed age distribution. Concerning gender, the percentage of male patients ranged between 30.4% and 75.2%.

Results of the +308A meta-analysis. The overall meta-analysis demonstrated a significant association between the TNF +308 A allele and psoriasis (OR = 0.74, 95%CI = 0.66-0.83, $P < 0.0001$). The corresponding forest plot in Figure 4.48 shows that individual odds ratios ranged between 0.28 and 1.60 with an outlier of 3.76. Still, a rather low between-study inconsistency was computed by Cochran Q test ($P = 0.075$) indicating the application of a fixed effects model. No signs for publication bias were found by funnel plot analysis (Figure 4.49) nor by Egger's regression test ($P = 0.2807$).

Table 4.16.: Characteristics of studies included in meta-analyses of TNF variants -308A and -238A in psoriasis

			Numbers		Frequencies -308A		Frequencies -238A			
Study [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**P**	**C**	**Age**	**M**
Settin 2009 [429]	Egypt	P (37%)	46	98	50.0	52.6	-	-	46.7 (15-70)	30.4
Magalhaes 2008 [296]	Brazil	P1	51	50	7.0	2.0	15.0	13.7	-	-
Craven 2001 [106]	UK (E)	P (58%)	81	66	13.6	17.4	-	-	-	41.7
Hohler 1997 [190] $^{\Phi 1}$	Ger (E)	P1	60	99	7.5	16.2	23.3	3.5	(22-79)	65.0
Nedoszytko 2007 [329]	Poland (E)	PV (81%)	166	65	7.8	15.4	13.9	3.1	37 (22-67)	50.6
Reich 2007 [391] $^{\Phi 2}$	Ger (E)	PV1	375	376	12.5	16.9	13.7	4.8	50 (12)	62.0
Chang 2007 [77] $^{\Phi 3 \Psi 1}$	Taiwan (A)	PV (49%)	170	210	5.9	9.5	4.4	1.9	52.1 (7-84)	72.4
Baran 2006 [26]	Poland (E)	PV (69%)	78	74	10.2	12.2	-	-	(19-?)	52.6
Long 2004 [288]	China (A)	PV (62%)	77	82	2.6	6.7	10.4	1.8	-	-
Tsunemi 2003 [484]	Japan (A)	PV	163	96	0.6	2.1	1.5	1.0	-	-
Chang 2003 [82] $^{\Psi 1}$	China (A)	PV (53%)	105	160	6.2	9.1	5.2	6.9	57.7 (11-84)	75.2
Reich 2002 [392] $^{\Psi 2}$	Ger (E)	PV (68%)	231	345	11.5	16.1	11.7	4.2	(11-92)	65.4
Reich 1999 [395] $^{\Psi 2}$	Ger (E)	PV (66%)	151	123	12.6	18.7	11.9	4.9	(11-92)	63.6
Jacob 1999 [216] $^{\Phi 1}$	Ger (E)	PV1	83	99	12.3	16.2	15.7	3.5	-	51.8
Subtotal			1599	1630	8.2	12.3	9.8	3.6		
Reich 2007 [391] $^{\Phi 2}$	Ger (E)	PA	376	376	12.8	16.9	9.3	4.8	46 (10)	60.0
Chang 2007 [77] $^{\Phi 3}$	Taiwan (A)	PA (74%)	102	210	3.4	9.5	3.4	1.9	45.6 (19-79)	52.0
Rahman-1 2006 [385]	Canada (E)	PA	237	103	18.4	18.9	10.7	5.3	50.1 (11.3)	51.0
Rahman-2 2006 [385]	Canada (E)	PA	203	101	16.0	19.3	8.8	5.9	50.5 (13.2)	59.0
Gonzalez 2002 [153]	Spain (E)	PA	81	110	31.0	21.0	18.0	12.0	48 (13)	60.5
Hohler 2002 [189] $^{\Phi 1 \Psi 3}$	Ger (E)	PA	89	99	5.2	16.2	17.2	3.5	47.8 (27-82)	52.8
Al-Heresh 2002 [3]	UK (E)	PA	124	101	21.0	16.3	9.3	6.9	54 (21-85)	48.4
Gonzalez 2001 [151]	Israel	PA	52	73	7.7	10.3	6.7	2.1	-	-
Hohler 1997 [190] $^{\Phi 1 \Psi 3}$	Ger (E)	PA (97%)	62	99	15.3	16.2	16.1	3.5	(34-82)	62.9
Subtotal			1326	1173	14.5	16.1	11.1	5.3		
Magalhaes 2010 [297]	Brazil	PVAGE $^{\#1}$	69	70	8.7	12.1	15.2	13.6	-	30.4
Mossner 2005 [314]	Estonia (E)	PVA $^{\#2}$	239	135	9.0	15.2	12.3	4.4	-	-
Kim 2003 [243]	Korea (A)	PVN (78%) $^{\#3}$	103	125	3.4	7.2	6.8	6.0	(12-83)	47.6
Mossner 2005 [314]	Estonia (E)	PPP	43	135	12.8	15.2	2.3	4.4	-	-
Total -308A			3617	2662	12.0	15.1				
Total -238A			3412	2424			11.0	5.7		

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Frequencies, frequencies of the -308 A allele and the -238 A allele in %; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Age, mean age of patients with standard deviation or range in brackets; Male, percentage of male patients in %; P, psoriasis without further specification; P1, early-onset psoriasis (Type 1); PV, psoriasis vulgaris; PV1, early-onset psoriasis vulgaris (Type 1); PA, psoriatic arthritis; PE, psoriatic erythroderma; PG, guttate psoriasis; NP, nummular psoriasis; PPP, palmoplantar pustulosis; PVAGE, psoriasis vulgaris, psoriatic arthritis, guttate psoriasis and psoriatic erythroderma; PVA, psoriasis vulgaris and psoriatic arthritis; PVN, psoriasis vulgaris and nummular psoriasis; $^{\#1}$, 7% PA, 4% PE, 3% PG; $^{\#2}$, 25% PA; $^{\#3}$, 70% NP; $^{\Phi 1-3}$, these studies use the same control subjects, respectively; $^{\Psi 1-3}$, these studies may show an overlap of study populations, respectively; - , data not provided in the article;

A stratification by psoriasis subtype indicated that the TNF +308 A allele was particularly associated with psoriasis vulgaris (OR = 0.66, 95%CI = 0.55-0.78, P < 0.0001) (Figure 4.50a). Between-study heterogeneity was lower than in the overall meta-analysis (P = 0.9619) and Egger's regression test showed a slight tendency to publication bias,

but remained insignificant (P = 0.0649) (Figure 4.51a). The independent results of Magalhaes et al 2010 [297] and Mossner et al 2005 [314], which involved a high percentage of psoriasis vulgaris patients in their mixed samples, were consistent with the outcome of the meta-analysis.

In contrast, association estimates for psoriatic arthritis did not remain significant (OR = 0.83, 95%CI = 0.61-1.12, P = 0.2219) (Figure 4.50b). A random effects model was applied, as inconsistency between studies was very high with two studies showing estimates in the opposite direction (P = 0.0056). There was no evidence of publication bias (Figure 4.51b). As the proportion of psoriatic arthritis was constantly low in mixed samples, these could not be used for comparison.

Concerning rare clinical psoriasis variants, the original studies on mainly (70%) nummular psoriasis and exclusively palmoplantar pustulosis did not detect a correlation of +308A with the respective disease, possibly indicating a different mode of inheritance.

As five studies investigated early- and late-onset psoriasis separately, additional meta-analyses according to onset type were performed, indicating a preferential association with early-onset psoriasis. In comparison to the overall meta-analysis, the association seemed to be even stronger reaching statistical significance (OR = 0.53 95%CI = 0.37-0.76, P = 0.0005) (Figure 4.52a). In contrast, none of the individual late-onset psoriasis cohorts reported an association and so did the meta-analysis (OR = 0.83, 95%CI = 0.54-1.27, P = 0.397) (Figure 4.52b). Fixed effects models were applied for both analyses due to low non-combinability of studies and there was no evidence of publication bias (Figure 4.53).

In addition, the hypothesis of a onset dependent correlation was supported by the highly significant results of exclusive early-onset cohorts by Hohler et al 1997 [190] and Reich et al 2007 [391]. The study of Nedoszytko et al 2007 [329] with 81% early-onset and the psoriatic arthritis study of Chang et al 2007 [77] with 74% early-onset were in favor of the hypothesis as well, while Magalhaes et al 2008 [296], Jacob et al 1999 [216] and Hohler et al 1997 [190] argued against it. Yet other characteristics like clinical psoriasis variant or ethnicity could act as potential confounders. For example, Magalhaes et al used unclassified Brazilian psoriasis patients while Hohler et al involved patients with additional joint involvement (Figure 4.48).

Stratification according to ethnicity was performed on psoriasis vulgaris samples only, based on two reasons. First, meta-analyses of different psoriasis subtypes had yielded deviating results and thus might cause bias. Second, 80% of psoriatic arthritis samples were from European origin while the distribution was more balanced for psoriasis vulgaris samples. The meta-analyses showed significant associations with both ethnicities, but with a slightly greater effect on Europeans (OR = 0.67, 95%CI = 0.56-0.81, P < 0.0001) (Figure 4.54a) than on Asians (OR = 0.57, 95%CI = 0.37-0.88, P = 0.0111) (Figure 4.54b). Fixed effects models were used in the analyses, as between-study heterogeneity was low and there were no signs of publication bias (Figure 4.55).

In contrast, all studies on ethnicities other than European and Asian showed negative results which might be due to potential confounding factors. For example, the psoriasis phenotype could play a certain role in the two Brazilian sample sets as the clinical subtype was either not specified or mixed. The Egyptian study of Settin et al 2009 [429]

involved a larger proportion of late-onset patients (63%) which might explain the lack of association and Gonzalez et al 2001 [151] used Israeli psoriatic arthritis patients, a clinical subtype which had shown negative reports earlier.

The mean frequency of the TNF +308 A allele was 15.1% among all healthy controls. The prevalence was higher in populations from European origin than from ethnic backgrounds. In detail, average frequencies of the TNF +308 A allele were 17.0% in Europeans and 6.9% in Asians while the frequency of the Israeli control samples lay in between (10.3%) and the two Brazilian control groups showed deviating values (2.0% and 12.1%). An outlier, however, was Egypt with an A allele frequency of 52.6%.

Discussion of the +308A meta-analysis. The performed meta-analysis tried to evaluate the genetic correlation of TNF +308A with psoriasis in different phenotypes and ethnicities. The frequency of the +308 A allele varied substantially in ethnic groups, being lowest in Asian and highest in Egyptian control samples with an average of 15%. Ethnicity-specific meta-analyses indicated significant associations with European and Asian populations, while there were only negative results for Brazilians, Egyptians and Israeli.

Stratification by clinical psoriasis subtypes indicated different modes of inheritance. While the relation of psoriasis vulgaris was highly significant in an additional meta-analysis, a correlation between the polymorphism and psoriatic arthritis could not be confirmed by means of meta-analysis. Three excluded studies were not able to detect an association with psoriatic arthritis either [4, 24, 165]. Concerning rare phenotypes, there was a negative report for palmoplantar pustulosis.

The direct comparison of early- and late-onset psoriasis in five studies showed a dependency on onset-type. Further early-onset or mainly early-onset studies supported the hypothesis of a preferential association with this onset-type before the age of 40 years, while others showed conflicting results. An excluded family study showed a negative result for early-onset psoriasis [216]. Yet these conflicting results might be influenced by confounding factors like psoriasis subtypes.

In conclusion, the present meta-analysis especially indicates a correlation between the TNF +308 A allele and early-onset psoriasis vulgaris in European and Asian populations which is consistent with the results of previous meta-analyses. Concerning different ethnicities and rare phenotypes, further research will be necessary to clarify conflicting results.

In addition to association analyses, the relevance of TNF as a potential candidate gene for psoriasis was examined by other research protocols. For example, an analysis reported elevated serum levels of tumor necrosis factor α in patients with psoriasis compared to healthy controls. The levels were independent from disease severity (PASI) and phototherapy, suggesting an systemic inflammation [9]. Relating to +308 A allele, there were both positive and negative reports relating to an influence on transcriptional activation and tumor necrosis factor α production. As TNF is mainly expressed in immune cells, an impaired secretion might lead to a disturbed immune response and predispose to psoriasis [227, 528].

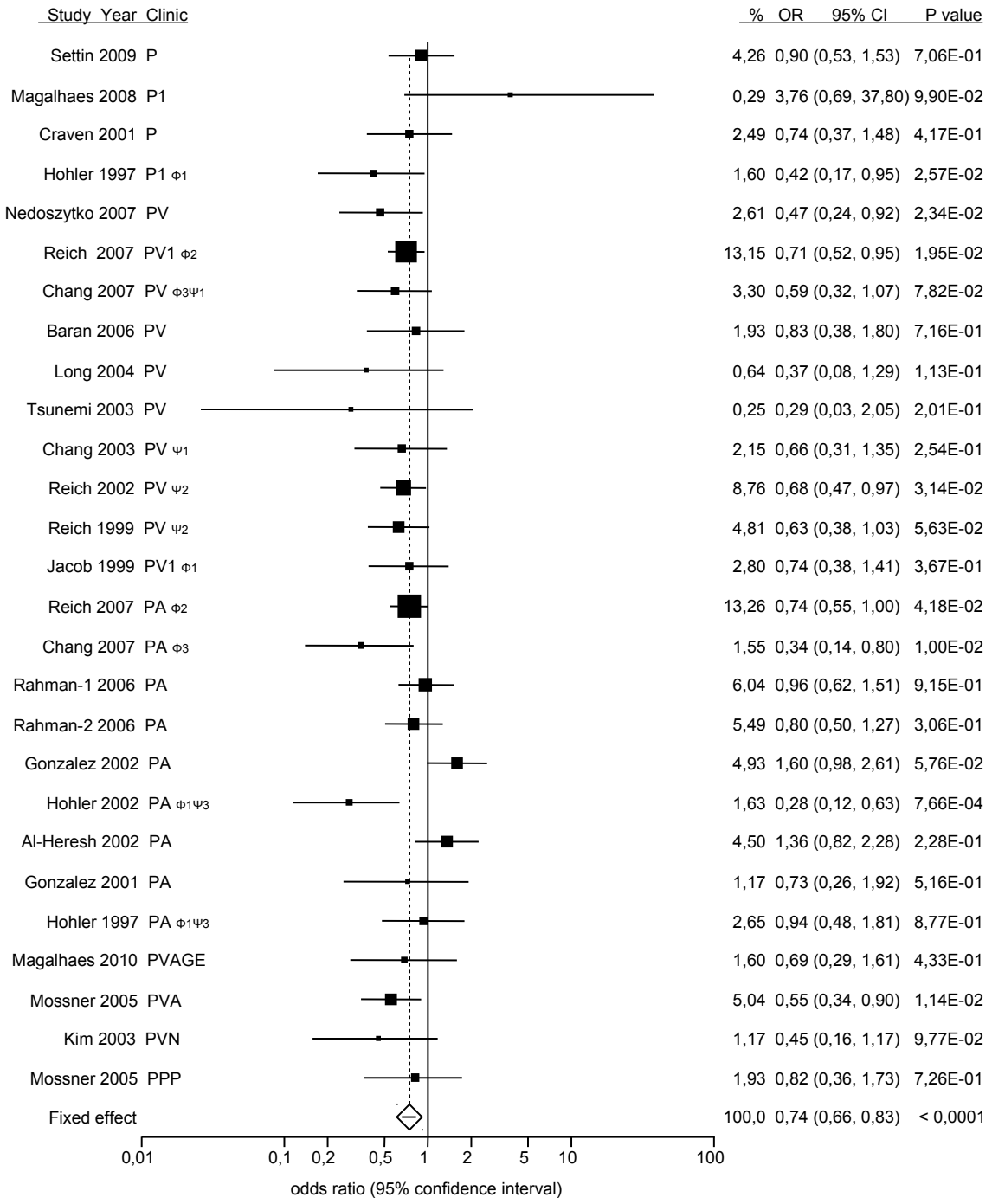


Figure 4.48.: Association of TNF -308 A allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.16.

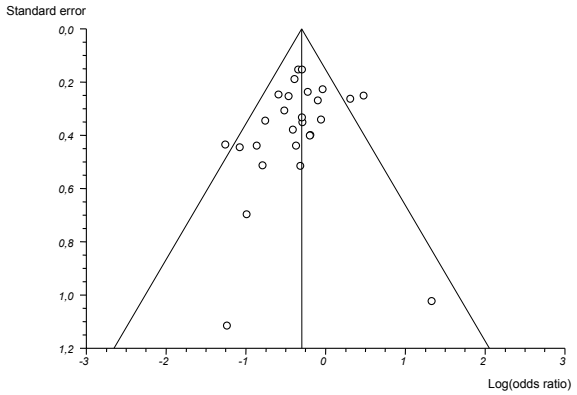
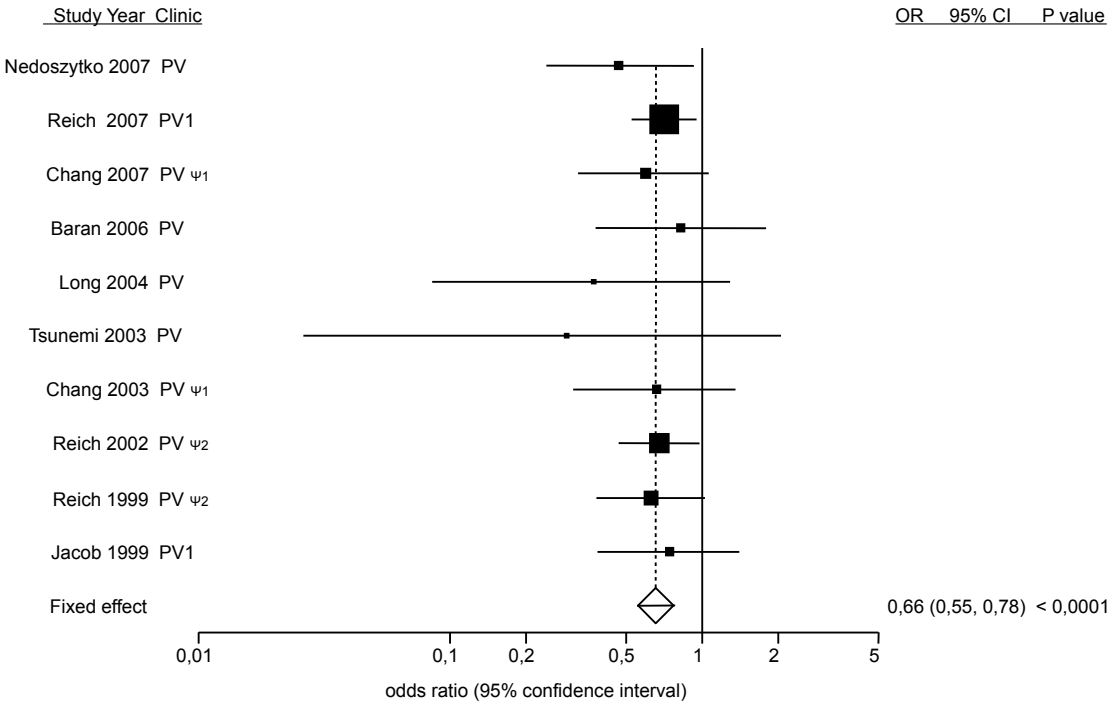
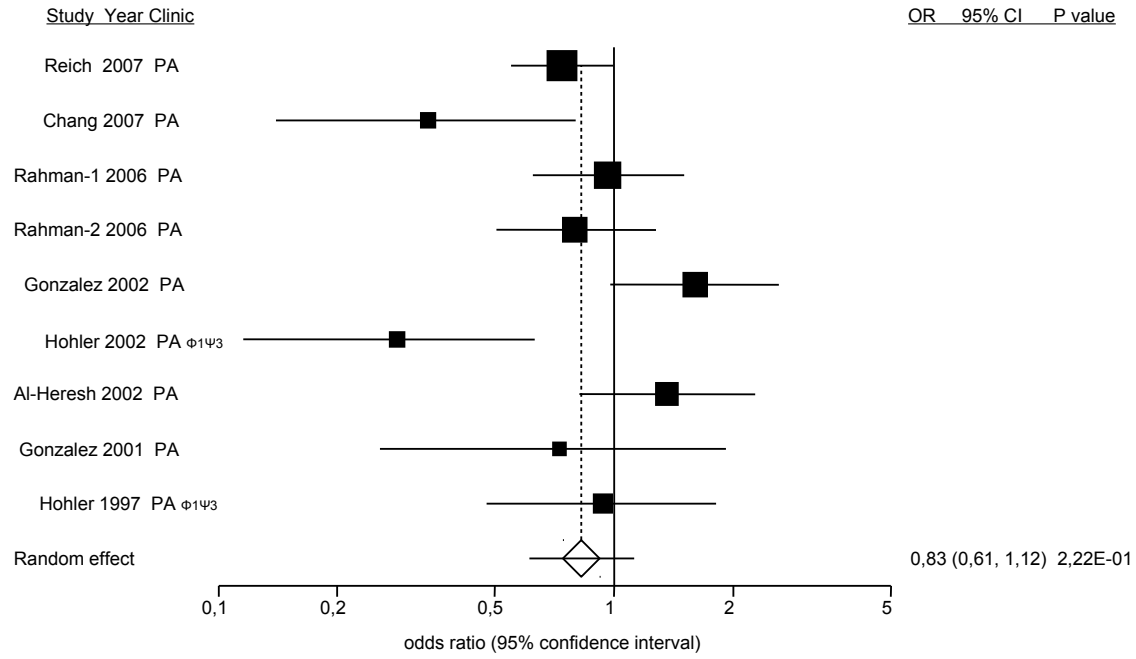


Figure 4.49.: Funnel plot showing log(OR) and standard error for the association of TNF -308 A allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.2807.

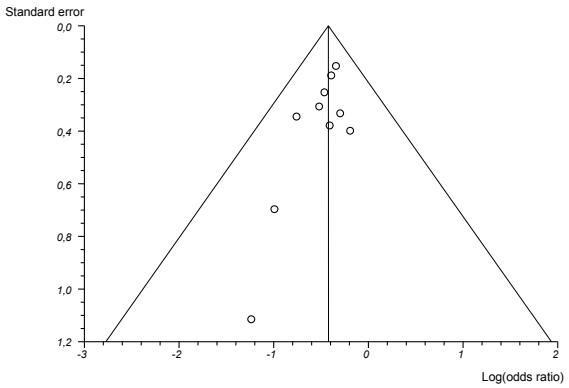


(a) Psoriasis vulgaris

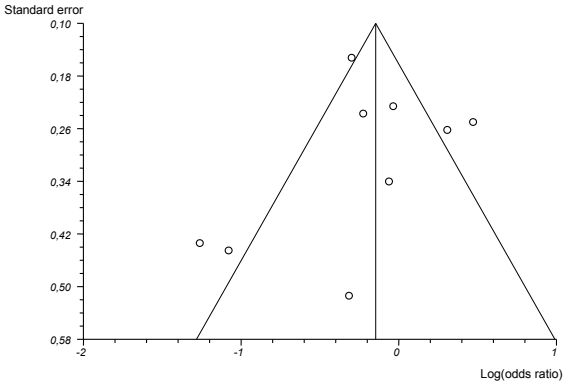


(b) Psoriatic arthritis

Figure 4.50.: Association of TNF polymorphism -308 A allele with (a) psoriasis vulgaris and (b) psoriatic arthritis. Forest plots showing ORs and 95% CIs for the studies (given by first author, year and country) included in the meta-analyses. Abbreviations see Table 4.16.

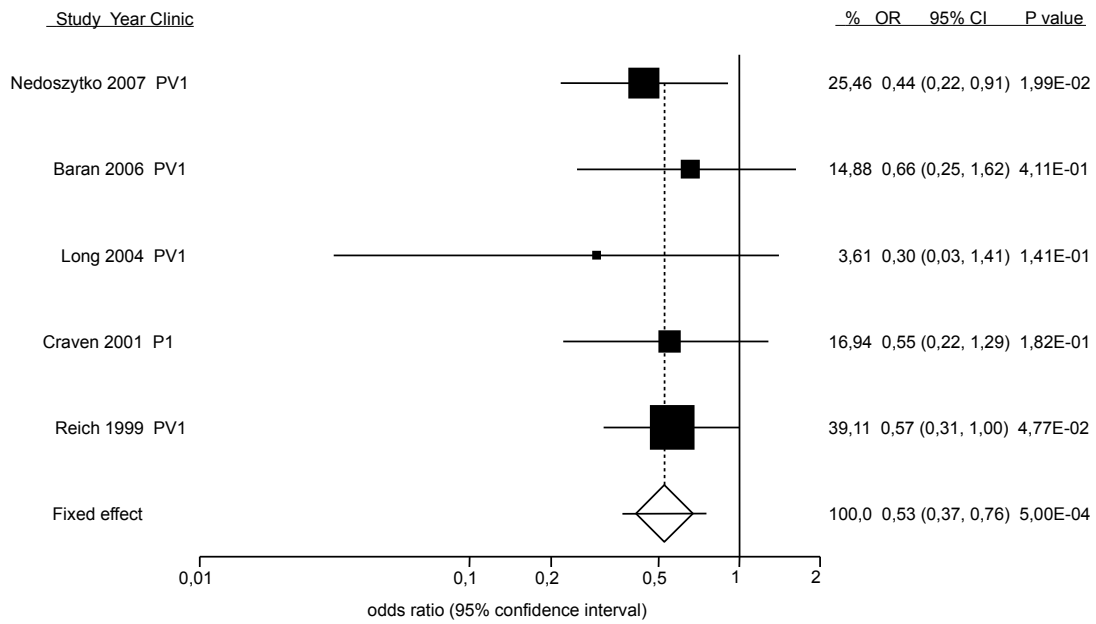


(a) Psoriasis vulgaris

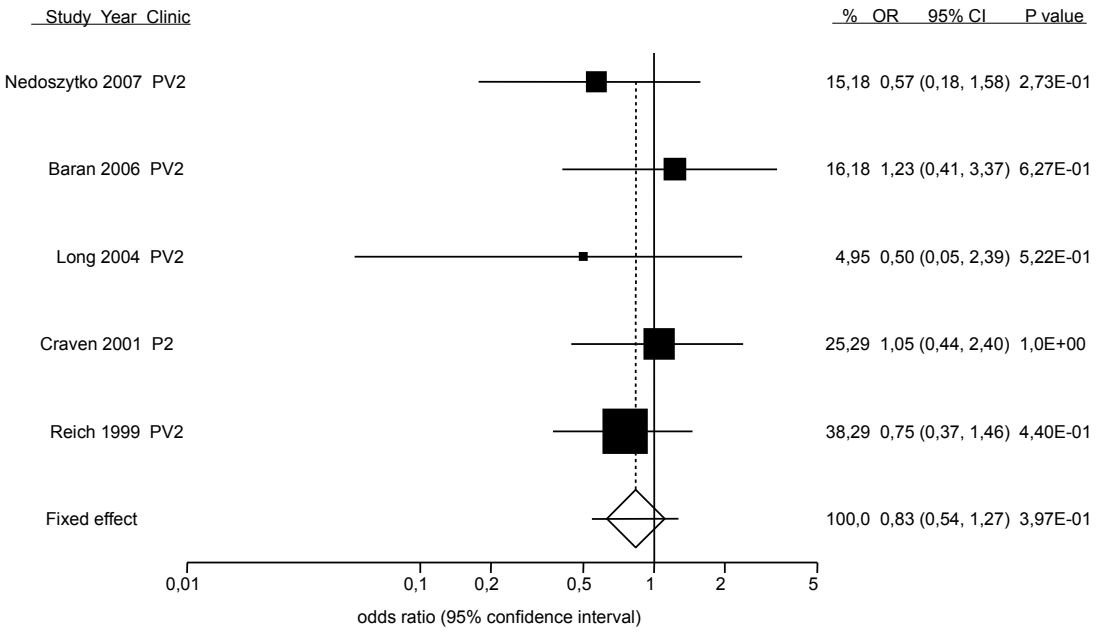


(b) Psoriatic arthritis

Figure 4.51.: Funnel plots showing log(OR)s and standard errors for the association of TNF polymorphism -308 A allele with psoriasis in (a) psoriasis vulgaris and (b) psoriatic arthritis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P values > 0.05; (a) $P = 0.0649$; (b) $P = 0.4517$.

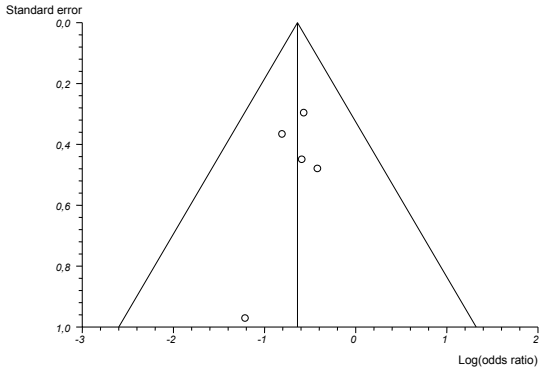


(a) Early-onset

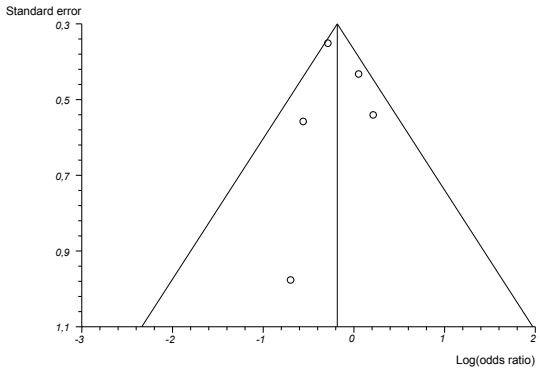


(b) Late-onset

Figure 4.52.: Association of TNF polymorphism -308 A allele with (a) early-onset and (b) late-onset psoriasis. Forest plots showing the ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analyses. Abbreviations see Table 4.16.

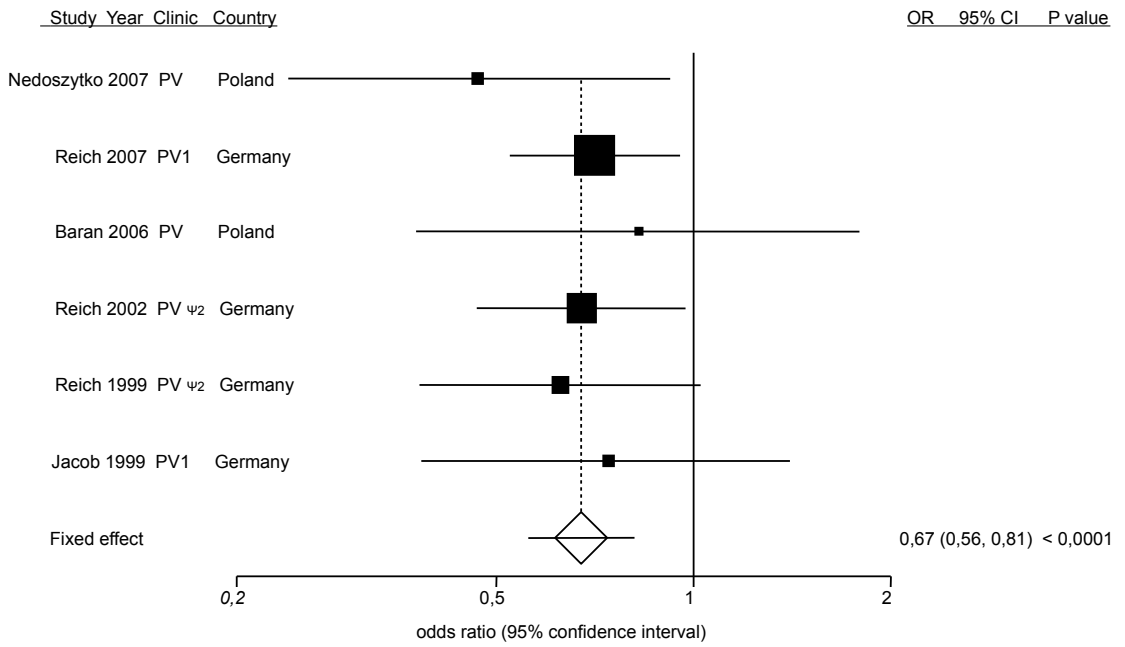


(a) Early-onset

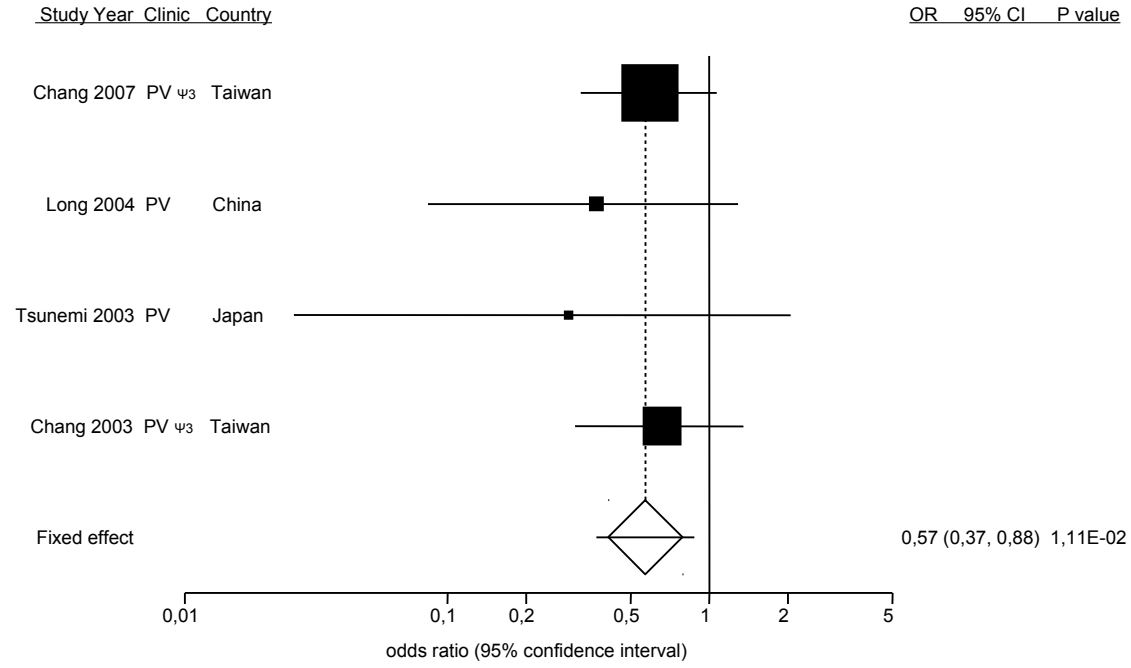


(b) Late-onset

Figure 4.53.: Funnel plots showing the log(OR)s and standard errors for the association of TNF polymorphism -308 A allele with (a) early-onset and (b) late-onset psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P values > 0.05; (a) P = 0.4407; (b) P = 0.6542.

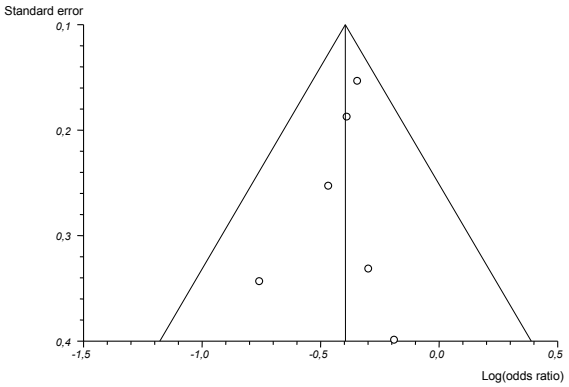


(a) Europe

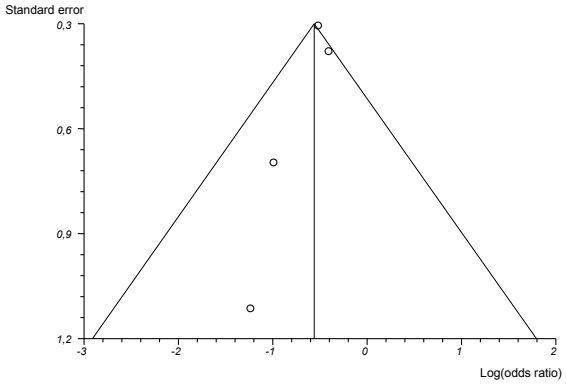


(b) Asia

Figure 4.54.: Association of TNF polymorphism -308 A allele with psoriasis vulgaris in (a) European and (b) Asian populations. Forest plots showing ORs and 95% CIs for the studies (given by first author, year, clinical psoriasis variant and country) included in the meta-analyses. Abbreviations see Table 4.16.



(a) Europe



(b) Asia

Figure 4.55.: Funnel plots showing log(OR)s and standard errors for the association of TNF polymorphism -308 A allele with psoriasis vulgaris in (a) European and (b) Asian populations. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P values > 0.05; (a) P = 0.6731; (b) P = 0.1041.

Meta-analysis of TNF +238A

Almost all studies on the association between TNF +308 A allele and psoriasis did an analysis of the +238 A allele as well. Only the case-control studies of Settin et al 2009 [429], Baran et al 2006 [26] and Craven et al 2001 [106] left out the additional variant.

Yet the two existing meta-analyses on the +308A polymorphism, investigated +238A as well. In this case, they confirmed an association between both psoriasis and psoriatic arthritis. Li et al 2007 [279] had included ten psoriasis vulgaris samples, six from Europe and four from Asia, finding an increased risk in both ethnicities.

Rahman et al 2006 [385] investigated eight psoriatic arthritis cohorts from Europe and one from Japan, showing that +238A was related to psoriatic arthritis in Europeans but not in Japanese. To give a full picture of the association with different clinical psoriasis variants and ethnicities, all samples of the previous meta-analyses and eight new cohorts were merged into a new meta-analysis.

Studies excluded from the +238A meta-analysis. As mentioned, a sequence analysis was carried out to identify polymorphisms the TNF gene by Nishibu et al 2002 [335]. Yet none of the sequenced 37 Japanese patients with psoriasis showed a genotype involving the +238 risk allele (AA or AG), but only the wild type GG.

A family-based association analysis by Jacob et al 1999 [216] was not able to detect a correlation between TNF +238A and psoriasis. The 83 German trios investigated by TDT did not show abnormalities in the transmission of the A allele from parents to their offspring with early-onset psoriasis.

A case-control study by Alenius et al 2004 [4] which used microsatellite markers to investigate the TNF locus, did not find an association between psoriatic arthritis and the said locus in 120 Swedish patients and 94 controls either.

Another case-control study by Arias et al 1997 [10] could not be included in the meta-analysis as the article was not publicly available. Yet they had reported a negative result for the +238A variant and 99 Caucasian psoriasis patients (65% early-onset) as well. The association analysis by Hamamoto et al 2000 [165] was excluded due to a different reason. The case-control data of 20 Japanese psoriatic arthritis patients and 87 healthy controls, did not reach a risk allele frequency of 1% for +238A. As the allele frequency was similarly low in patients and controls, no significant association was detected.

Studies included in the +238A meta-analysis. The remaining 20 studies consisted of 24 cohorts with a total of 3412 cases and 2424 controls. Table 4.16 lists the cohorts according to clinical psoriasis variant and presents some characteristics. The major part of the studies investigated the commonest phenotypes psoriasis vulgaris and psoriatic arthritis. Two additional studies did not state the exact phenotype of their samples, while three involved a mixture of different phenotypes and one consisted of palmoplantar pustulosis only.

About half of the studies stated the percentage of early-onset psoriasis among all cases. Most of them involved more early-onset subjects than late-onset subjects, four even included exclusively patients with a disease onset before the age of 40 years. Only

Chang et al 2003 [82] and Chang et al 2007 [77] had a balanced early-onset/late-onset ratio. A direct comparison between the two different onset types was provided in three studies [329, 288, 395].

The major part of the studies were carried out on subjects form Europe or from European origin. Nearly 80% of psoriatic arthritis cohorts and 50% of psoriasis vulgaris cohorts were Europeans. The other half of the psoriasis vulgaris group consisted of Asian samples, while there was only one Asian psoriatic arthritis cohort. The remaining studies involved samples from Brazil and Israel.

The age of participants ranged between childhood and old age with no studies on children only, but some on adults only. Yet one third of the studies did not provide information on the age of participants. However, reports on both early- and late-onset psoriasis might show a mixed age distribution. Concerning gender, the percentage of male patients ranged between 30.4% and 75.2%.

Results of the +238A meta-analysis. The overall meta-analysis implied an increased risk for psoriasis imparted by the TNF +238A variant (OR = 2.29, 95%CI = 1.80-2.91, P < 0.0001) (Figure 4.56). Individual odds ratios ranged from 1.11 to 8.30 with the exception of two outliers, 0.75 and 0.51. This high between-study heterogeneity was confirmed by Cochran Q test (P = 0.0023) and led to the application of a random effects model. Signs for publication bias were no detected by funnel plot analysis (Figure 4.57) nor by Egger's regression test (P = 0.9732).

Stratification by psoriasis subtype indicated that the TNF +238 A allele was significantly associated with both psoriasis vulgaris (OR = 2.80, 95%CI = 2.19-3.58, P < 0.0001) (Figure 4.58a) and psoriatic arthritis (OR = 2.09, 95%CI = 1.63-2.67, P < 0.0001) (Figure 4.58b). Fixed effects models were applied here, as between-study inconsistency was low in the separate analyses and no tendency to publication bias was observed (Figure 4.59).

Relating to rare psoriasis phenotypes, in contrast, the original publication of Kim et al 2003 [243] on mainly nummular psoriasis did not detect an association. The same applies for the palmoplantar pustulosis sample of Mossner et al 2005 [314].

In order to investigate a putative dependency on onset types, three studies investigated early- and late-onset psoriasis separately. The corresponding allele frequencies and association estimates were summarized in Table 4.17 to allow a side-by-side comparison. Significant evidence of association with the +238A variant was only provided for the overall samples and early-onset subgroups. The late-onset subgroups, however, did not show significant results.

This potential onset dependent correlation was reflected by significant results of exclusive early-onset psoriasis samples like Reich et al 2007 [391] and Jacob et al 1999 [216]. Solely the early-onset cohort of Magalhaes et al 2008 [296] does not appear to confirm this hypothesis. Yet the lack of association could be due to ethnicity as both Brazilian cohorts show insignificant results.

In addition, two mainly early-onset psoriasis cohorts favor of the hypothesis of an onset-type dependent association by reaching highly significant results. The cohort of

Table 4.17.: Association of TNF variant -238A with psoriasis according to onset type

				Association		
Study [Ref]	**Type**	**Number**	**Frequency**	**OR**	**95%CI**	**P value**
Nedoszytko 2007 [329]	P1	134	16.8	6.36	2.23-24.82	3.26E-05
	P2	32	1.6	0.50	0.01-5.21	1.00E+00
	P1+P2	166	13.9	5.07	1.79-19.75	3.86E-04
Long 2004 [288]	P1	48	15.6	9.94	2.68-54.59	4.12E-05
	P2	29	1.7	0.94	0.02-12.00	1.00E+00
	P1+P2	77	10.4	6.22	1.72-33.85	1.42E-03
Reich 1999 [395]	P1	100	14.0	3.17	1.51-7.04	1.28E-03
	P2	51	7.8	1.66	0.57-4.57	3.13E-01
	P1+P2	151	11.9	2.64	1.30-5.70	3.74E-03

Study, studies given by first author and year of publication; Ref, reference number; Type, onset type of psoriasis; P1, early-onset psoriasis (Type 1); P2, late-onset psoriasis (Type 2); Numbers, numbers of patients and controls; P, patients; C, controls; Frequency, frequency of the TNF -238 A allele given in %; OR, odds ratio, 95%CI, confidence interval; P value, calculated by Fisher's exact test;

Nedoszytko et al 2007 [329] involved 81% while the psoriatic arthritis cohort of Hohler et al 1997 [190] involved 97% early-onset patients with disease manifestation before the age of 40 years.

Stratification according to ethnicity was performed on psoriasis vulgaris samples only, as clinical psoriasis subtypes might act as potential confounders. Moreover, the psoriasis vulgaris group showed a balanced composition consisting of five European samples and four Asian samples, while 80% of the psoriatic arthritis group were European.

After stratification, a significant association could only be detected for European populations (OR = 3.23, 95%CI = 2.46-4.24, $P < 0.0001$) (Figure 4.60a), while it lost significance for Asian samples (OR = 1.54, 95%CI = 0.88-2.69, P = 0.1276) (Figure 4.60b), indicating a different mode of inheritance. Fixed effects models were used as between-study heterogeneity was low and Egger's regression test did not show signs of publication bias for the individual meta-analyses (Figure 4.61).

Similarly, none of the other studies on different ethnicities showed positive results. Gonzalez et al 2001 [151] did not find an association between Israeli subjects and the TNF +238A variant, while results for two Brazilian samples were negative as well. Yet for the latter samples of Magalhaes et al 2008 [296] and Magalhaes et al 2010 [297] the clinical subtype could be a confounding factor as the one sample was not classified and the other was mixed.

The mean frequency of the TNF +238 A allele was 5.7% among all control populations. It did not differ much between Europeans (5.0%) and Asians (3.5%), while the prevalence was a bit lower in controls from Israel (2.1%) and a lot higher in controls from Brazil (13.7%).

Discussion of the +238A meta-analysis. The present meta-analysis supported a significant relation between TNF +238A and psoriasis. Yet the frequency of the +238 A allele varied substantially between different countries and ethnicities, being highest in Brazilian control populations. Additional meta-analyses indicated a significant association for Europeans only, but not for Asians and the two original reports on Brazilian samples did not show an association either.

Stratification by psoriasis subtypes did not reveal any dependency, especially no differences between presence and absence of joint involvement. Significant relations to psoriasis vulgaris and psoriatic arthritis were confirmed by separate meta-analyses. Two excluded studies were not able to confirm an association with psoriatic arthritis, yet one of them was carried out on Japanese subjects with Asian background [4, 165]. Relating to rare phenotypes, there were negative results for nummular psoriasis and palmoplantar pustulosis in the original reports.

Further stratification by onset types indicated a significant association with early-onset rather than late-onset psoriasis. Direct comparisons in three studies and additional significant results of exclusive or mainly early-onset studies supported the hypothesis. Solely one early-onset cohort from Brazil lacked association and an excluded family study showed a negative result for early-onset psoriasis [216]. Yet these conflicting results might be influenced by confounding factors like ethnicity and psoriasis subtypes.

In conclusion, the performed meta-analysis favors a correlation between TNF +238 A allele and early-onset psoriasis vulgaris as well as psoriatic arthritis in European populations which is consistent with the results of previous meta-analyses for the most part. Li et al 2007 [279] had found a significant association with Asian samples as well. Further research will be necessary to clarify these conflicting results.

In addition to association analyses, the relevance of TNF as a potential candidate gene for psoriasis was examined by other research protocols. For example, elevated serum levels of tumor necrosis factor α were observed in patients with psoriasis compared to healthy control subjects. The levels were independent from disease severity (PASI) and phototherapy, suggesting an systemic inflammation [9]. In addition, the +238 A allele seems to have a significant effect on tumor necrosis factor α production and as TNF is mainly expressed in immune cells an impaired secretion might lead to a disturbed immune response and predispose to psoriasis [227].

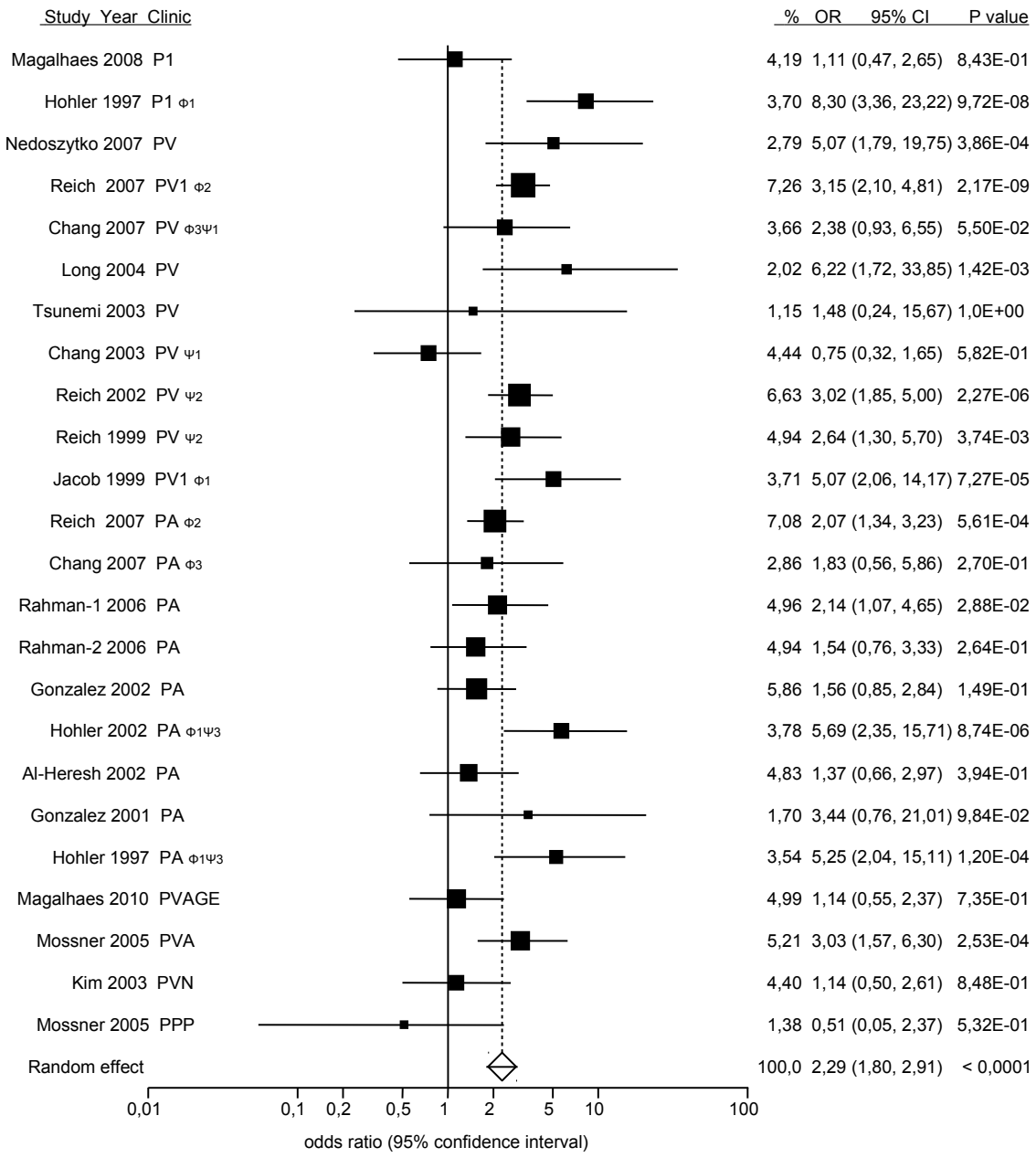


Figure 4.56.: Association of TNF -238 A allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.16.

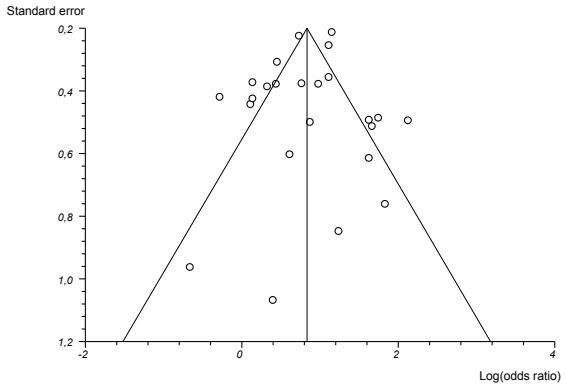
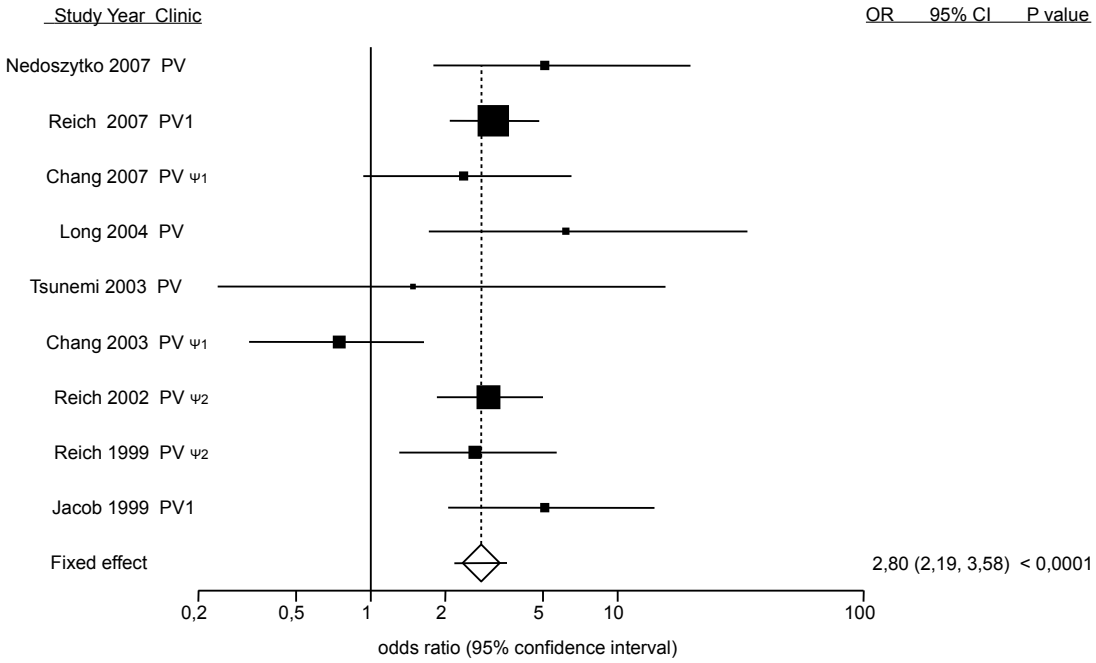
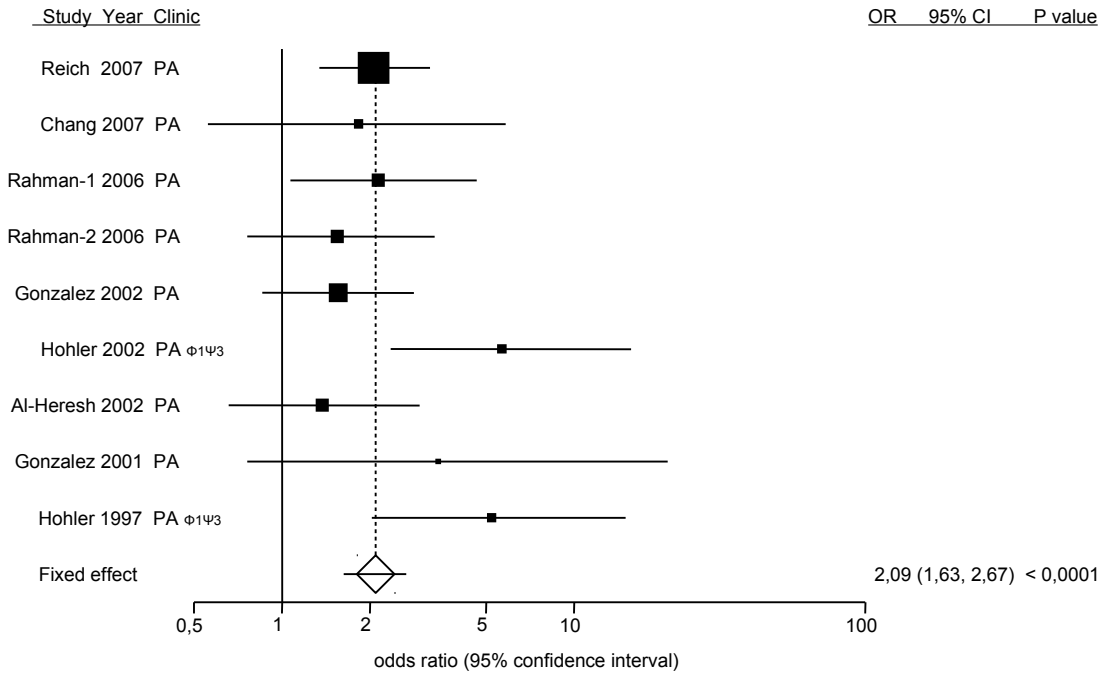


Figure 4.57.: Funnel plot showing log(OR) and standard error for the association of TNF -238 A allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.9732.

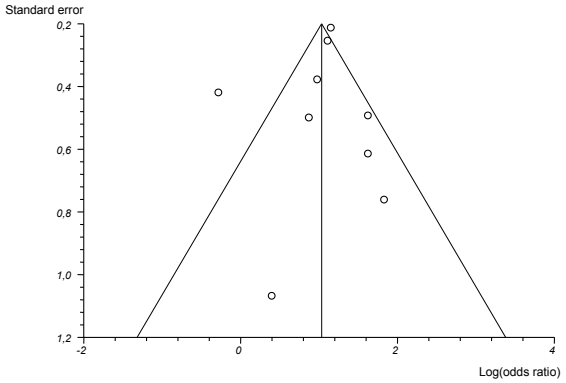


(a) Psoriasis vulgaris

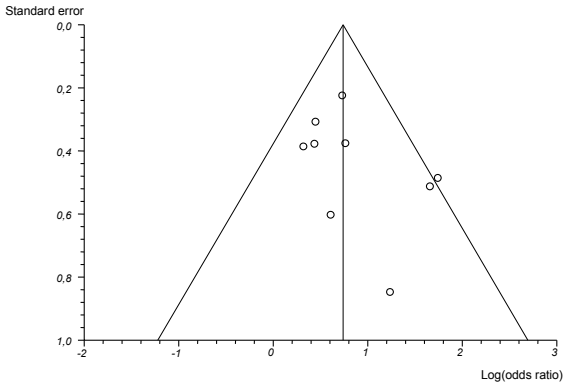


(b) Psoriatic arthritis

Figure 4.58.: Association of TNF polymorphism -238 A allele with (a) psoriasis vulgaris and (b) psoriatic arthritis. Forest plots showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analyses. Abbreviations see Table 4.16.

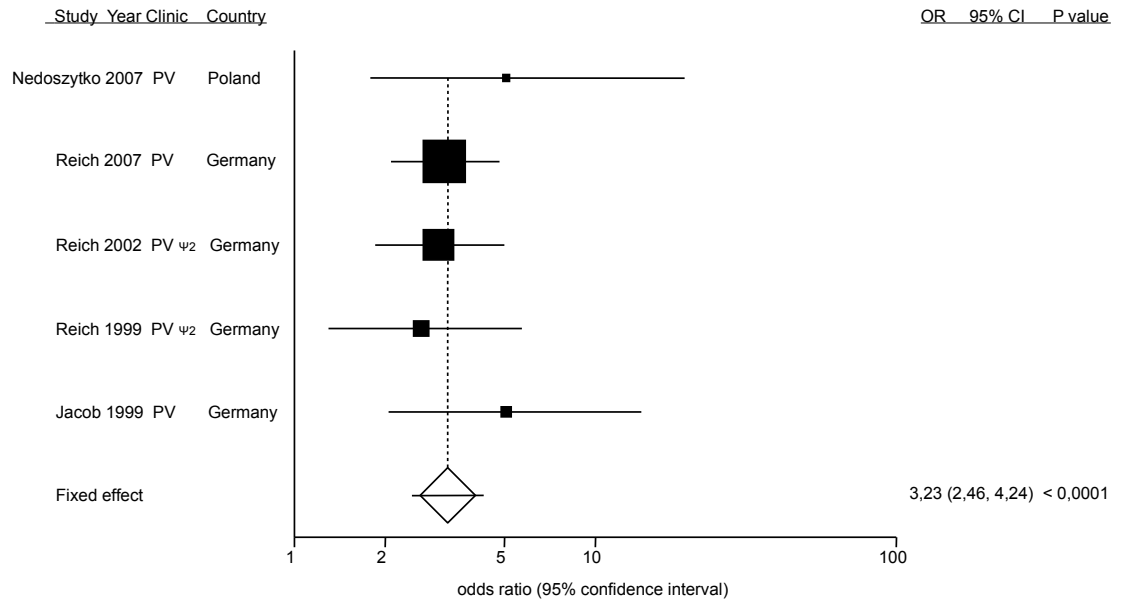


(a) Psoriasis vulgaris

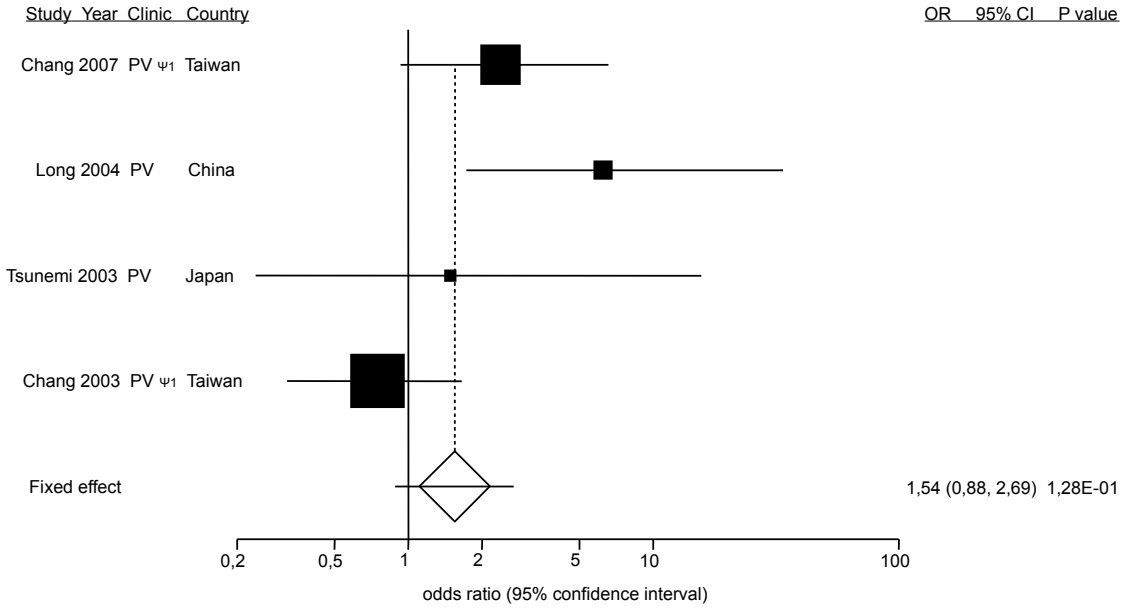


(b) Psoriatic arthritis

Figure 4.59.: Funnel plots showing log(OR)s and standard errors for the association of TNF polymorphism -238 A allele with psoriasis in (a) psoriasis vulgaris and (b) psoriatic arthritis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P values > 0.05; (a) $P = 0.9281$; (b) $P = 0.2613$.

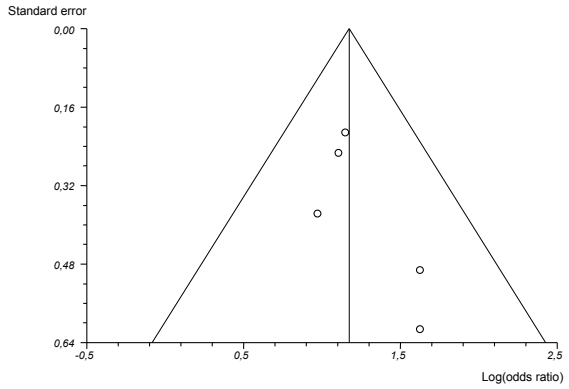


(a) Europe

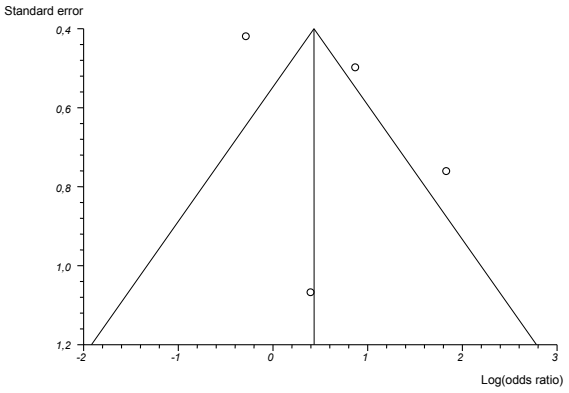


(b) Asia

Figure 4.60.: Association of TNF -238 A allele with psoriasis vulgaris in (a) European and (b) Asian populations. Forest plots showing ORs and 95% CIs for the studies (given by first author, year, clinical psoriasis variant and country) included in the meta-analyses. Abbreviations see Table 4.16.



(a) Europe



(b) Asia

Figure 4.61.: Funnel plots showing log(OR)s and standard errors for the association of TNF -238 A allele with psoriasis vulgaris in (a) European and (b) Asian populations. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P values > 0.05; (a) P = 0.213; (b) P = 0.4561.

Meta-analysis of TNF -857T

In addition to the two discussed TNF variants, a third variant was investigated in at least six case-control studies involving eight independent cohorts. Yet only Niizeki et al 2000 [334] investigated the association between +857T and psoriasis exclusively, independent from +308A and +238A.

Studies included in the -857T meta-analysis. As none of the said case-control data had to be excluded the meta-analysis comprises eight cohorts with 1563 cases and 1452 controls. For each study the leading author, year of publication, country, clinical psoriasis variant, number of patients and controls, allele frequencies, mean age of patients, mean age at onset and percentage of male patients are reported in Table 4.18.

The major part of cohorts involved patients with psoriatic arthritis. Two additional studies investigated psoriasis vulgaris and one palmoplantar pustulosis. Concerning different onset types, the psoriasis vulgaris sample of Reich et al 2007 [391] consisted of early-onset patients only while Chang et al 2007 [77] provided information about the percentage of early-onset cases in their psoriatic arthritis (74%) and psoriasis vulgaris (49%) samples. Except for Reich et al 2007 [391] none of the studies provided the mean age at onset of the involved patients.

The mean age at enrollment was fairly homogeneous, ranging from 44 to 52 years. The female/male ratio was either balanced or in favor of male subjects from 51% to 72.4%. Only Hamamoto et al 2000 [165] did not provide further information on the characteristics of their sample. Concerning ethnicity, one half of the populations were from European origin, while the other half came from Asian countries.

Results of the -857T meta-analysis. The performed meta-analysis yielded a pooled association estimate of 1.37 (95%CI = 1.15-1.64, P = 0.0004) by applying a fixed effects model. In spite of two outliers that can be observed in the forest plot (Figure 4.62), Cochran Q test did not indicate a significant between-study heterogeneity (P = 0.06). Concerning publication bias, Egger's regression test did not show any deviation from the symmetry assumption (P = 0.3052) and so did the funnel plot analysis (Figure 4.63).

A total of three different clinical psoriasis variants were involved in the meta-analysis and psoriatic arthritis was investigated most frequently. A separate analysis of this phenotype alone yielded an even higher and more significant association estimate of 1.60 (95%CI = 1.25-2.03, P = 0.0001) with a lower variance between the individual studies.

In contrast, only one of the original reports on psoriasis vulgaris provided a positive result. The study on palmoplantar pustulosis yielded an insignificant association estimate in the opposite direction, indicating a different mode of inheritance for this rare psoriasis variant. When this study was excluded from the meta-analysis an enhanced effect was observed for the remaining studies (OR = 1.49, 95%CI = 1.24-1.80, P < 0.0001) and the inconsistency decreased.

A qualified statement on putative dependency on onset type cannot be given, as data is insufficient. Concerning gender, no influence was seen either. Relating to ethnicity,

Table 4.18.: Characteristics of studies included in meta-analysis of TNF variant -857T in psoriasis

			Numbers		Frequency				
Study [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**Age**	**Onset**	**Male**
Reich 2007 [391] $^{\Phi 1}$	Germany (E)	PV1	375	376	11.5	7.6	50 (12)	23 (11)	62.0
Chang 2007 [77] $^{\Phi 2}$	Taiwan (A)	PV (49%)	170	210	10.6	10.2	52.1 (7-84)	-	72.4
Reich 2007 [391] $^{\Phi 1}$	Germany (E)	PA	376	376	13.0	7.6	46 (10)	30 (13)	60.0
Chang 2007 [77] $^{\Phi 2}$	Taiwan (A)	PA (74%)	102	210	15.7	10.2	45.6 (19-79)	-	52.0
Rahman-1 2006 [385]	Canada (E)	PA	237	103	6.8	7.8	50.1 (11.3)	-	51.0
Rahman-2 2006 [385]	Canada (E)	PA	203	101	14.8	8.4	50.5 (13.2)	-	59.0
Hamamoto 2000 [165]	Japan (A)	PA	20	87	17.5	15.5	-	-	-
Niizeki 2000 [334]	Japan (A)	PPP	80	575	13.8	17.7	44 (25-70)	-	60.0
Total			1563	1452	13.0	11.2			

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Frequency, frequency of the -857 T allele in %; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Age, mean age of patients with standard deviation or range in brackets; Onset, mean age at onset with standard deviation or range in brackets; Male, percentage of male patients in %; PV, psoriasis vulgaris; PV1, early-onset psoriasis vulgaris (Type 1); PA, psoriatic arthritis; PPP, palmoplantar pustulosis; $^{\Phi 1-2}$, these studies use the same control subjects, respectively; - , data not provided in the article;

however, three out of four studies on subjects from European ancestry showed significant associations with -857T, while all Asian samples did not (compare Table 4.18 and Figure 4.62). Allele frequencies differed significantly as well, with the -857 T allele being less frequent in European (7.9%) than in Asian control populations (14.5%).

Discussion of the -857T meta-analysis. The present meta-analysis demonstrated an association between the -857 T allele and psoriasis. A separate analysis of psoriatic arthritis alone, supported a significant correlation to this phenotype in particular. For psoriasis vulgaris data was insufficient and for palmoplantar pustulosis, a different genetic association can be discussed as the only original study yielded an insignificant estimate in the opposite direction.

Due to insufficient data, no statement on the influence of onset types can be given. In contrast, an ethnicity dependent association was observed. While the outcome for populations from European origin was significant, none of the four Asian cohorts provided proof of association.

In summary, an association between the TNF -857 T allele and European psoriatic arthritis patients in particular could be seen in the present meta-analysis. Still, the significant outcome for -857T variant might be due to the proximity to the other highly significantly associated TNF variants +308A and +238A. The functional relevance of TNF as a candidate gene for psoriasis was discussed earlier.

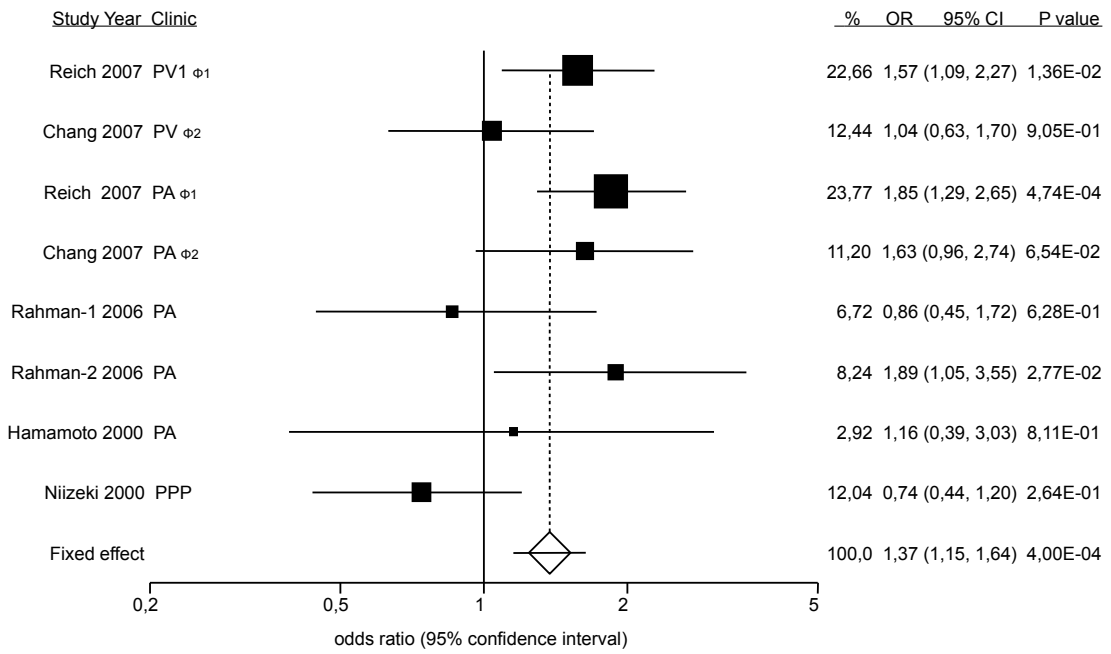


Figure 4.62.: Association of TNF polymorphism -857 T allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.18.

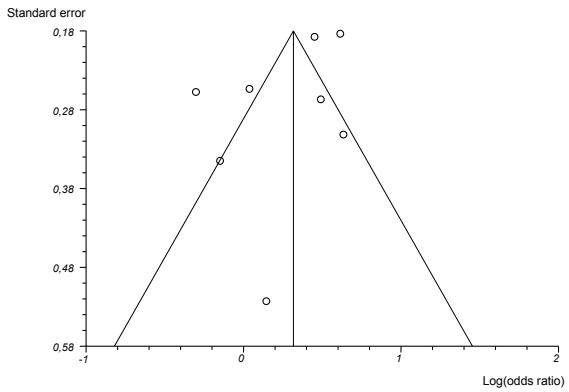


Figure 4.63.: Funnel plot showing log(OR) and standard error for the association of TNF polymorphism -857 T allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.3052.

4.2.14. SNP n.9 intergenic variant rs10456057

The single nucleotide polymorphism number 9 lies in a regulatory region [303] 4 kb centromeric to HLA-C within the PSORS1 locus [503]. Initially, it was used as a marker SNP in a family-based analysis trying to achieve a high-resolution genetic characterization of the the major susceptibility locus for psoriasis [503]. The association was more significant than for any previous SNP in this region. Consequently, the SNP was tested in several replication samples, even if itself does not seem likely as a disease-causing variant.

Studies excluded from the meta-analysis. Helms et al 2005 [177] performed both a case-control study included in the meta-analysis and a family study that had to be excluded. The TDT analysis showed a significant over-transmission of the G allele to affected children in 242 Caucasian nuclear families from the United States.

Studies included in the meta-analysis. As none of the identified case-control studies had to be excluded, the meta-analysis comprises seven cohorts with 1296 cases and 1178 controls. For each study the leading author, year of publication, country, clinical variant of psoriasis, numbers and variant allele frequencies of patients and controls, mean age at onset (with standard deviation or range) and percentage of male patients for all cohorts are reported in Table 4.19.

The involved studies differed from each other in some of their characteristics. For example, concerning the country where the participants reside and their ethnicity. There were two cohorts with Asian background from Taiwan and three with European ancestry from Italy, the United Kingdom and the United states. The participants of the two remaining cohorts resided in Israel and India, respectively. The percentage of male patients reached from 44.1% to 70.2%, thus showing a wide range.

In addition, study samples displayed different clinical psoriasis variants. Psoriasis vulgaris, the most common form, was investigated by Chang et al 2004 [81], Orru et al 2005 [357], Chang et al 2006 [76] as well as Veal et al 2002 [503] while Martinez-Borra et al 2005 [303] studied exclusively early-onset psoriasis vulgaris. The samples of Asumalahti et al 2003 [16] suffered from guttate psoriasis, a rare subtype of psoriasis which can be further classified into acute guttate psoriasis alone and a guttate flare of psoriasis vulgaris. Helms et al 2005 [177] state that 20% of the subjects may have had additional joint involvement, not specifying the underlying psoriasis variant.

Concerning mean ages at disease onset, these were consistently whenever provided ranging from 17.5 years in the guttate psoriasis cohort of Asumalahti et al 2003 [16] to 30.4 years in the psoriasis vulgaris cohort of Orru et al 2005 [357]. As mentioned, Martinez-Borra et al 2005 [303] studied exclusively early-onset psoriasis with a mean age at onset of 27.4 years. In addition, Chang et al 2004 [81] and Chang et al 2006 [76] studied early- and late-onset psoriasis patients independently of each other, providing a direct comparison of the two onset-types.

Table 4.19.: Characteristics of studies included in meta-analysis of SNP n.9 rs10456057 polymorphism in psoriasis

			Numbers		Frequency			
Study [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**Onset**	**Male**
Chang 2006 [76] $^{\Psi}$	Taiwan (A)	PV (52%)	178	203	16.9	6.4	$\leq 40 \leq$	70.2
Martinez-Borra 2005 [303]	Israel	PV1	59	79	43.2	33.5	27.4 (13.9)	66.1
Orru 2005 [357]	Italy (E)	PV	161	160	37.9	25.0	30.4 (18.8)	44.1
Chang 2004 [81] $^{\Psi}$	Taiwan (A)	PV (52%)	115	103	18.7	6.3	$\leq 40 \leq$	68.7
Veal 2002 [503]	India	PV	77	77	40.0	25.0	-	-
Helms 2005 [177] ^{cau}	US (E)	PPA $^{\#1}$	572	247	40.0	13.0	23	-
Asumalahti 2003 [16]	UK (E)	PG $^{\#2}$	134	309	50.0	11.0	17.5	-
Total			1296	1178	35.2	17.2		

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Frequency, frequency of the SNP n.9 rs10456057 polymorphism in %; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Onset, mean age at onset with standard deviation or range in brackets; $\leq 40 \leq$, patients with onset before and after 40 years (early- and late-onset psoriasis) involved; Male, percentage of male patients in %; P, psoriasis without further specification; PV, psoriasis vulgaris; PV1, early-onset psoriasis vulgaris (Type 1); PA, psoriatic arthritis; PG, guttate psoriasis; PPA, psoriasis without further specification and psoriatic arthritis; ^{cau}, the control group referred to as *CAU* was chosen for calculations; $^{\Psi}$, these studies may show an overlap of study populations; $^{\#1}$, 20% may have additional PA; $^{\#2}$, acute PG (64.48%) alone or guttate flare of PV (56.42%); - , data not provided in the article;

Results of the meta-analysis. The performed meta-analysis on all studies yielded an association estimate of 3.00 (95%CI = 1.86-4.84, P < 0.0001) by applying a random effects model (Figure 4.64). Odds ratios in the individual studies ranged from 1.51 to 8.09, reflecting the large between-study heterogeneity of 88.1% (inconsistency I^2) with Chochran Q test showing a highly significant result (P <0.0001). Egger's regression test and funnel plot analysis did not show a deviation from the symmetry assumption (P = 0.3891), thus not indicating publication bias (Figure 4.65).

The study of Asumalahti et al 2003 [16] which investigated cases suffering from guttate psoriasis achieved the highest association estimate, indicating an pronounced effect in this rare psoriasis phenotype. When the study was excluded from the meta-analysis a lower overall association estimate (OR = 2.52, 95%CI = 1.70-3.73, P < 0.0001) with a lower but still significant between-study heterogeneity (P = 0.0004) was observed.

The second highest odds ratio was achieved by the sample of Helms et al 2005 [177]. One might speculate that this is due to psoriatic arthritis subtypes included in the sample, but as barely 20% of the participants show joint involvement this explanation seems unlikely. The fact that mean age at onset is comparatively low (23 years), makes a correlation to that feature of the disease thinkable. This would match with the even lower mean age at onset (17.5 years) in the guttate psoriasis cohort of sumalahti el al 2003 [16]. In contrast, Martinez-Borra et al 2005 [303] showed the weakest association (OR = 1.51) of all studies in spite of investigating exclusively early-onset subjects. Still, the mean age at onset was higher (27.4 years) compared to the other two studies.

Table 4.20.: Association of SNP n.9 rs10456057 polymorphism with psoriasis according to onset type

				Association		
Study [Ref]	**Type**	**Number**	**Frequency**	**OR**	**95%CI**	**P value**
Chang 2006 [76]	P1	92	22.3	4.19	2.40-7.40	8.23E-08
	P2	86	11.0	1.82	0.92-3.52	6.29E-02
	P1+P2	178	16.9	2.96	1.79-5.01	5.86E-06
Chang 2004 [81]	P1	60	26.7	5.40	2.59-11.72	5.88E-07
	P2	55	10.0	1.65	0.64-4.15	2.68E-01
	P1+P2	115	18.7	3.41	1.73-7.13	9.50E-05

Study, studies given by first author and year of publication; Ref, reference number; Type, onset type of psoriasis; P1, early-onset psoriasis (Type 1); P2, late-onset psoriasis (Type 2); Numbers, numbers of patients and controls; P, patients; C, controls; Frequency, frequency of the SNP n.9 rs10456057 polymorphism given in %; OR, odds ratio, 95%CI, confidence interval; P value, calculated by Fisher's exact test;

As mentioned, Chang et al 2004 [81] and Chang et al 2006 [76] studied early- and late-onset psoriasis patients independently of each other. Table 4.20 reports corresponding numbers of patients, allele frequencies, odds ratios, 95% confidence intervals and p values for each subgroup and the combined analysis. Both early-onset groups showed higher allele frequencies and higher association estimates while the association estimates in the late-onset groups lost their significance. This outcome supports the thesis of onset dependent genetic association. Still, the level of evidence remains low as the studies of Chang et al might show an overlap in study populations.

There was one striking observation regarding different ethnicities: Allele frequencies were notably lower in Asian control populations (6.35%) compared to the remaining populations including subjects from Europe, Israel and the United States (21.5%). But even if the SNP n.9 rs10456057 variant allele showed different frequencies in different populations, similar association estimates were observed across countries and ethnicities. Yet the findings on Asian populations are based on the reports of Chang et al 2004 and 2006 [81, 76], which might show an overlap of study populations, only.

Discussion of the meta-analysis. The present meta-analysis demonstrated a significant association of SNP n.9 rs10456057 and psoriasis. In addition, excluded family data showed positive results as well [177]. The highest association estimate in the meta-analysis was observed in a study on guttate psoriasis which could be due to different reasons. Either is there in fact a higher genetic influence in guttate psoriasis than in common psoriasis variants or other characteristics cause the effect. Especially the low mean age at onset of the patients seems a likely candidate.

Two observations are in favor of this hypothesis. First, another cohort showing low mean age at onset achieved the second highest association estimate (Helms et al 2005 [177]). Second, the studies by Chang et al 2004 and 2006 [81, 76] provided higher odds ratios for early-onset patients than for late-onset patients in a direct comparison with

the latter even loosing significance. But as the study populations might overlap, this result should not be overrated.

Especially as another cohort of exclusively early-onset psoriasis patients showed the weakest association estimate of all studies. Yet one possible explanation would be underestimation due to small sample size, another would be a different mode of inheritance in Jewish samples from Israel. Additionally, the mean age at onset is higher than in Helms et al 2005 [177] and Asumalahti et al 2003 [16]. Still, a putative dependency on age at onset has to be validated in further studies.

In spite of the highly significant outcome of the present meta-analysis, the SNP n.9 is unlikely to be a disease-causing allele lying in a regulatory region [303]. Being in near complete linkage disequilibrium with HLA-Cw*0602 [76], it supports HLA-C as psoriasis risk gene in the PSORS1 locus. As additional genetic factors within the MHC have been assumed [318], emphasis has to be placed on functional analyses to track down disease-causing variants.

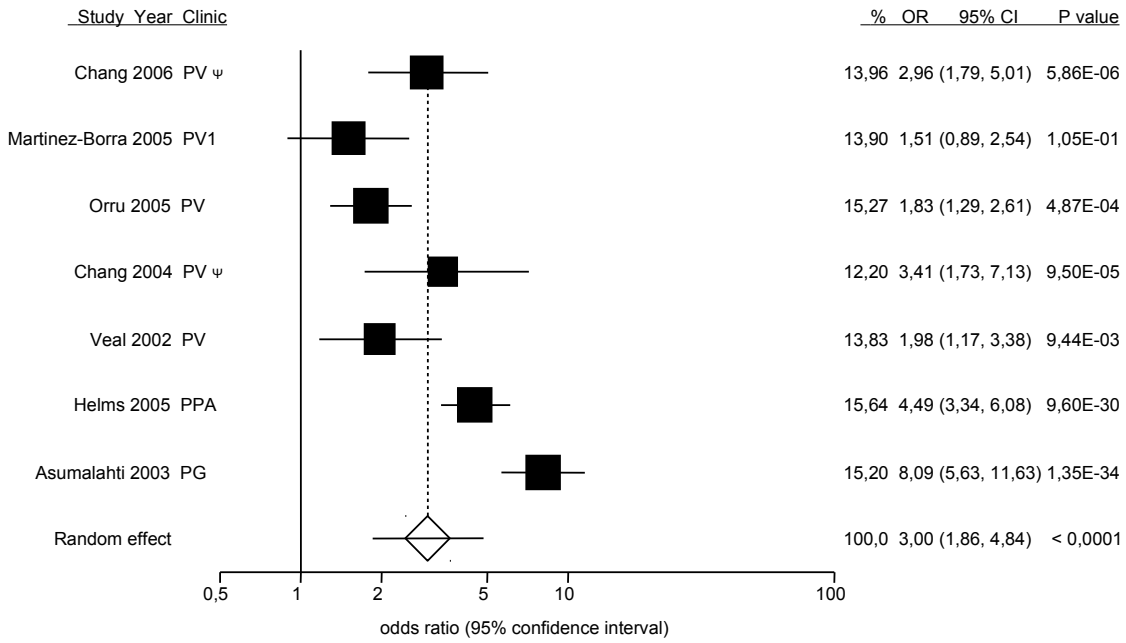


Figure 4.64.: Association of SNP n.9 rs10456057 C allele with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.19.

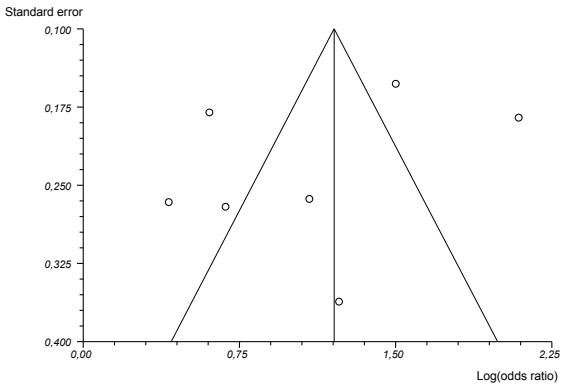


Figure 4.65.: Funnel plot showing log(OR)s and standard errors for the association of SNP n.9 rs10456057 C allele with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.3891.

4.2.15. CCHCR1 haplotype HCR*WWCC

The CCHCR1 gene was mapped to the PSORS1 risk locus on chromosome 6p21.3. As it contains 16 exons and is highly polymorphic, a putative role as a candidate gene was suspected [17]. Consequently, a large number of coding single nucleotide polymorphisms and haplotypes have been tested for association with psoriasis over the past decade.

Genetic variants like 251T, 256T and 1285T are only a few examples for positive reports (Table B.1, p 235). By far the highest number of positive reports, was achieved for the conserved susceptibility allele HCR*WWCC consisting of 307T, 325T, 1723T and 2327G. Accumulated case-control data was sufficient to perform a meta-analysis.

Studies excluded from the meta-analysis. Several association studies could not be included in the meta-analysis for the simple fact that they did not investigate the HCR*WWCC haplotype as a whole, but separate SNPs. Asumalahti et al 2002 [19], for example, found associations to 307T, 325T, 1723T and 2327G polymorphisms separately in a family cohort of 419 European and Indian subjects.

One year later they tried to replicate their findings for rare phenotypes (Asumalahti et al 2003 [16]). A sample consisting of 134 guttate psoriasis cases and matched controls from the UK showed associations with the four polymorphisms forming HCR*WWCC 307T, 325T, 1723T and 2327G. Two cohorts comprising 156 palmoplantar pustulosis cases from the UK and Sweden, in contrast, failed to detect an association. Combined analyses for the HCR*WWCC haplotype by Asumalahti et al 2002 and 2003 [19, 16] were included in the meta-analysis.

Two more studies investigated the association of SNPs 325T and 2327G. Allen et al 2005 [6] tested the findings of the previous studies in a late-onset psoriasis cohort including 145 cases from the United Kingdom, aggregating additional evidence for association. Meanwhile, Lascorz et al 2005 [267] could not replicate these results in two German psoriasis samples with and without joint involvement (375 and 281 cases, respectively).

Three studies analysed the association of psoriasis with other haplotypes. Chia et al 2001 [90] performed an analysis risk haplotypes including HCR-251T and HCR-269T. They found that a haplotype cluster carrying the TT allele at HCR conferred a high relative risk. Holm et al 2003 [194] reported a significant association with a haplotype called HCR*WW in 87 Swedish psoriasis cases and Chang et al 2005 [80] in 73 Taiwanese early-onset psoriasis cases. Yet none of the two studies stated the exact composition of HCR*WW.

Studies included in the meta-analysis. Finally, five case-control studies including seven cohorts investigated the association of HCR*WWCC with psoriasis. These cohorts comprised a total of 1521 cases and 1051 controls. For each study the leading author, year of publication, country, clinical variant of psoriasis, numbers and variant allele frequencies of patients and controls, mean age at onset (with standard deviation or range) and percentage of male patients for all cohorts are reported in Table 4.21.

The involved studies and their cohorts differ from each other in several points. First, most samples resided in European countries like Germany, Finland and the United King-

Table 4.21.: Characteristics of studies included in meta-analysis of HCR*WWCC in psoriasis

			Numbers		Frequency			
Study [Ref]	**Country**	**Clinic**	**P**	**C**	**P**	**C**	**Onset**	**Male**
Asumalahti 2002 [19]	Japan (A)	P $^{\#1}$	83	70	9.6	1.4	36 (1-65)	68.7
Reich 2007 [391] $^{\Phi 1}$	Germany (E)	PV1	375	376	36.4	19.5	23 (11)	62.0
Chang 2006 [76]	Taiwan (A)	PV	178	203	16.0	6.1	40	70.2
Reich 2007 [391] $^{\Phi 1}$	Germany (E)	PA	376	376	30.8	19.5	30 (13)	60.0
Suomela 2007 [459] $^{\Phi 2}$	Finland (E)	PA	66	93	43.9	19.0	24 (1-40)	66.7
Suomela 2007 [459] $^{\Phi 2}$	Finland (E)	PVG	309	93	66.3	19.0	20 (0-40)	56.0
Asumalahti 2003 [16]	UK (E)	PG $^{\#2}$	134	309	81.0	31.0	17.5	45.0
Total			1521	1051	40.6	15.4		

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Frequency, frequency of HCR*WWCC in % ; Clinic, clinical psoriasis variant/s; Onset, mean age at onset with standard deviation or range in brackets; Male, percentage of male patients in %; P, psoriasis without further specification; PV, psoriasis vulgaris; PV1, early-onset psoriasis vulgaris (Type 1); PA, psoriatic arthritis; PG, guttate psoriasis; PVG, psoriasis vulgaris and guttate psoriasis; $^{\Phi 1-2}$, these studies use the same control subjects, respectively; $^{\#1}$, 52% psoriasis vulgaris; $^{\#2}$, 56% guttate flare of psoriasis vulgaris; - , data not provided in the article;

dom. Only two cohorts had an Asian background coming from Japan or Taiwan. The percentage of male patients reached from 45.0% to 70.2%, thus showing a wide range.

Concerning psoriasis phenotypes, the samples show a mixed picture of different clinical psoriasis variants. Chang et al 2006 [76] and Reich et al 2007 [391] studied a psoriasis vulgaris cohort each. The sample of Asumalahti et al 2002 [19] involved 52% psoriasis vulgaris patients while Suomela et al 2007 [459] studied mixed phenotypes comprising psoriasis vulgaris and guttate psoriasis. Asumalahti et al 2003 [16] involved exclusively guttate psoriasis, in which 56% of the patients had a guttate flare of psoriasis vulgaris. Last but not least, two studies investigated psoriatic arthritis cohorts.

Concerning different onset types, all but three patients in the psoriasis vulgaris cohort of Reich et al 2007 [391] suffered from early-onset disease. Similarly, both samples of Suomela et al [459] had an onset of disease before the age of 40 while all other samples showed a low mean ages at onset as well (Table 4.21). A direct comparison between early- and late-onset psoriasis was performed by Chang et al 2006 [76].

Results of the meta-analysis. The overall meta-analysis yielded a highly significant result, supporting an association between HCR*WWCC and psoriasis (OR = 3.96, 95%CI = 2.30-6.82, $P < 0.0001$) (Figure 4.66). Every single study had been able to detect an association with individual odds ratios ranging from 1.84 to 9.45. In total, between-study heterogeneity was highly significant (Cochran Q test, $P < 0.0001$) which led to the application of a random effects model. There were no signs for publication bias, neither in the funnel plot (Figure 4.67) nor in Egger's regression test ($P = 0.2818$).

Interestingly, the guttate psoriasis cohort of Asumalahti et al 2003 [16] achieved the highest association estimate and the mixed study including psoriasis vulgaris and guttate psoriasis yielded the second highest. This indicates a pronounced effect for the rare phenotype. Relating to the remaining psoriasis phenotypes, no difference of association estimates between psoriasis vulgaris and psoriatic arthritis were observed.

According to onset types, only the study by Chang et al 2006 [76] studied early- and late-onset psoriasis independently (P1: OR = 4.37, 95%CI = 2.49-7.77, P = 5.88E-08; P2: OR = 1.56, 95%CI = 0.76-3.14, P = 2.14E-01). The direct comparison showed that the association remained significant for early-onset psoriasis only.

In addition, all other study groups involved in the meta-analysis showed low mean ages at onset together with significant results (Table 4.21). This favors the hypothesis of an onset-dependent association, but data is not sufficient to draw a final conclusion to this question.

Regarding different ethnicities, allele frequencies were notably lower in Asian control populations from Taiwan and Japan (3.8%) compared to European control populations from Germany, Finland and the UK (23.2%). In spite of this, similar results concerning association estimates were achieved across ethnicities.

Discussion of the meta-analysis. The present meta-analysis demonstrated a significant association between HCR*WWCC and psoriasis. In addition, most of the excluded studies reported positive associations with separate SNPs and other haplotypes as well. The association of HCR*WWCC did not seem to depend on characteristics like clinical psoriasis subtype, gender or ethnicity. Only a dependency on onset type was suspected, but data was insufficient to validate this hypothesis.

As the CCHCR1 gene shares the PSORS1 locus with a number of other putative candidate genes, it might be a marker lying near the real susceptibility gene. While it had been promoted as the PSORS1 risk gene in 2002 [19], current research indicates HLA-Cw*0602, which is in strong LD with HCR*WWCC, as PSORS1 candidate gene number one [324, 318, 130].

Still, there might be additional risk factors nearby and thus functional analyses are of high importance. For HCR*WWCC, a deviating secondary-structure and a differing expression in psoriatic lesions was shown [19]. In addition, its was found to promote keratinocyte proliferation [19] and regulate transcription factor binding [101]. It might also contribute to the up-regulation of proteins like keratins or SPRRs in psoriasis [122].

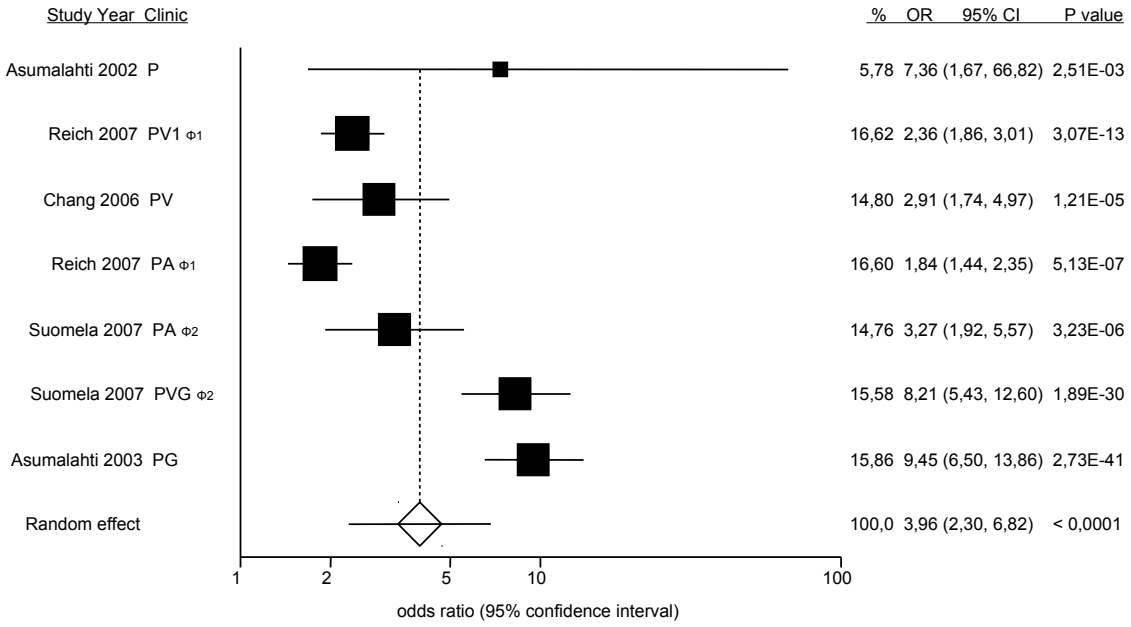


Figure 4.66.: Association of HCR*WWCC with psoriasis. Forest plot showing the ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. Abbreviations see Table 4.21.

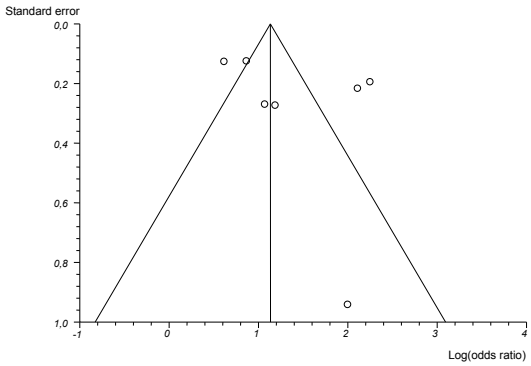


Figure 4.67.: Funnel plot showing the log(OR)s and standard errors for the association of HCR*WWCC with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.2818.

4.2.16. HLA-B allele B*57

The HLA-B gene lies within the PSORS1 locus on chromosome 6p21.3 as well. Over the past decade, many putative risk alleles have been tested for association with psoriasis (Table 4.1, p. 56). Especially the HLA-B57 allele was suggested, first reported by Hohler et al 1996 [191] analysing the corresponding antigen. Subsequently, a total of thirteen association studies were conducted in order to replicate this finding. The respective results were summarized and validated by means of meta-analysis.

Studies excluded from the meta-analysis. The association studies by Hohler et al 1996 [191], Jenisch et al 1998 [219], Atasoy et al 2006 [20] and Feng et al 2009 [132] did not analyse the genetic variant itself but the encoded product. This means that they detected HLA-B antigens, representing the alleles, through respective antibodies. All of them showed significant associations between the HLA-B57 antigen and psoriasis.

In addition, Schmitt-Egenolf et al 2001 [422] conducted a family study on 52 German early-onset psoriasis patients and their parents. They found a significant over-transmission of the HLA-B*5701 allele.

Studies included in the meta-analysis. The meta-analysis involves ten case-control studies with 1154 cases and 1617 controls. For each study the leading author, year of publication, country, clinical variant of psoriasis, numbers and variant allele frequencies of patients and controls, mean age at onset (with standard deviation or range) and percentage of male patients are reported in Table 4.22.

There are several differences to be considered between the involved studies. For example, the cohorts came from a lot of different countries and ethnicities. There were three samples from Europe, one from North America, two from Latin America, two from Israel and one from Thailand. The percentage of male patients showed a wide range reaching from 30.4% to 66.1%.

Concerning psoriasis phenotypes, a variety of different clinical psoriasis variants were investigated. Psoriasis vulgaris was analysed by the studies of Martinez-Borra et al 2005 [303], Choonhakarn et al 2002 [94] and Gonzalez et al 2000 [152]. Two of them studied exclusively early-onset psoriasis vulgaris patients and one in the major part (68%). The samples of Grubic et al 2004 [160], Gonzalez et al 2002 [153] and Gonzalez et al 2001 [151] suffered from psoriatic arthritis, while Magalhaes et al 2010 [297] used a mixed group consisting of psoriasis vulgaris, psoriatic arthritis and guttate psoriasis. Two more studies by Biral et al 2006 [40] and Helms 2005 [177] did not specify the clinical phenotype and thus cannot be classified.

In addition to the exclusively or mainly early-onset psoriasis vulgaris cohorts, most subjects of Biral et al 2006 [40] had received their diagnosis before the age of 40 years (76%) as well. While the mean age at onset of the Helms et al 2005 [177] cohort was rather low, all psoriatic arthritis cohorts showed a rather high mean age at onset (Table 4.22). A direct comparison between early- and late-onset subjects was performed by Biral et al 2006 [40] and Choonhakarn et al 2002 [94].

Table 4.22.: Characteristics of studies included in meta-analysis of HLA-B57 polymorphism in psoriasis

			Numbers		Frequency			
Study [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**Onset**	**Male**
Biral 2006 [40]	Brazil (LA)	P (76%)	92	160	8.7	1.9	-	44.6
Helms 2005 [177] ^{cau}	US (E)	P	436	460	15.0	4.0	23.0	-
Atasoy 2006 [20]	Turkey	PV (69%)	72	104	44.4	3.8	-	59.7
Martinez-Borra 2005 [303]	Israel	PV1	59	79	2.5	1.9	27.4 (13.9)	66.1
Choonhakarn 2002 [94]	Thailand (A)	PV (68%) $^{\#1}$	140	300	4.3	1.0	-	-
Gonzalez 2000 [152] $^{\Omega}$	Spain (E)	PV1	95	104	17.8	5.7	26.9 (15.1)	41.1
Grubic 2004 [160]	Croatia (E)	PA	58	157	10.3	1.5	33.8 (19-54)	48.3
Gonzalez 2002 [153] $^{\Omega}$	Spain (E)	PA	81	110	14.0	6.0	31 (11)	60.5
Gonzalez 2001 [151]	Israel	PA	52	73	11.5	4.1	36.4 (15.7)	-
Magalhaes 2010 [297]	Brazil (LA)	PVAG $^{\#2}$	69	70	8.7	2.2	-	30.4
Total			1154	1617	13.7	3.2		

Study, given by first author and year of publication; Ref, reference number; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Frequency, frequency of the HLA-B57 allele in %; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Onset, mean age at onset with standard deviation or range in brackets; Male, percentage of male patients in %; P, psoriasis without further specification; PV, psoriasis vulgaris; PV1, early-onset psoriasis vulgaris (Type 1); PA, psoriatic arthritis; PVAG, psoriasis vulgaris, psoriatic arthritis and guttate psoriasis; ^{cau}, the control group named *CAU* was used for the meta-analysis; $^{\Omega}$, these studies may show an overlap of control populations; $^{\#1}$, 99% PV, 1% PG/PPP; $^{\#2}$, 7.3% PA; - , data not provided in the article;

Results of the meta-analysis. The present meta-analysis on all studies yielded a highly significant result (OR = 4.56, 95%CI = 3.52-5.91, P < 0.0001) (Figure 4.68). A homogeneous picture was presented by individual odds ratios ranging in a small scale from 2.56 to 7.13 except form the studies by Atasoy et al 2006 [20] (OR = 20.00) and Martinez-Borra et al 2005 [303] (OR = 1.35). The latter was the only study being not able to detect an association. In total, the between-study heterogeneity remained insignificant (Cochran Q test, P = 0.0585), leading to the application of a fixed effects model. There was no evidence of publication bias neither in the funnel plot analysis (Figure 4.69) nor in Egger's regression test (P = 0.9644).

The most likely explanation for the insignificant result of Martinez-Borra et al 2005 [303] is a small sample size as no other characteristics of the study stick out. The homogeneous shape of the forest plot (Figure 4.68) does not imply dependency on ethnicity or clinical psoriasis variant. It is only noticeable that the studies with the lowest odds ratios show the highest percentages of male patients. However, the study with the highest odds ratio does not preferably use women (48% males) making a dependency on gender unlikely.

Biral et al 2006 [40] and Choonhakarn et al 2002 [94] studied early- and late-onset psoriasis patients independently of each other. Table 4.23 reports corresponding numbers of patients, allele frequencies, odds ratios, 95% confidence intervals and p values for each subgroup and the combined analysis. Whereas Biral et al 2006 [40] achieved significant

Table 4.23.: Association of HLA-B57 with psoriasis according to onset type

				Association		
Study [Ref]	**Type**	**Number**	**Frequency**	**OR**	**95%CI**	**P value**
Biral 2006 [40]	P1	70	10.7	6.28	2.23-20.13	8.91E-05
	P2	22	9.1	31.90	3.00-1575.00	8.60E-04
	P1+P2	92	8.7	4.98	1.81-15.80	4.95E-04
Choonhakarn 2002 [94]	P1	95	5.0	5.50	1.78-18.63	1.06E-03
	P2	45	2.0	2.25	0.22-12.82	2.81E-01
	P1+P2	140	4.3	4.43	1.52-14.53	3.22E-03

Study, studies given by first author and year of publication; Ref, reference number; Type, onset type of psoriasis; P1, early-onset psoriasis (Type 1); P2, late-onset psoriasis (Type 2); Numbers, numbers of patients and controls; P, patients; C, controls; Frequency, frequency of the HLA-B57 allele given in %; OR, odds ratio, 95%CI, confidence interval; P value, calculated by Fisher's exact test;

results for both subgroups, the analysis of Choonhakarn et al 2002 [94] remained significant for early-onset subjects only. Together with the fact that another early-onset cohort did not reach statistical significance in the meta-analysis, no preferable association to any onset type can be assumed.

Allele frequencies in controls ranged from 1.0% to 6.0% and tended to be elevated in subjects from European descent except for the Croatian cohort. But in spite of deviating frequencies of the HLA-B57 allele in different populations, similar results concerning association estimates were achieved across countries and ethnicities. Yet data was limited as some populations have only been studied once or twice.

Discussion of the meta-analysis. The performed meta-analysis indicated a significant association between HLA-B57 and psoriasis, which is in conformity with the positive reports of all excluded studies. In addition, the association seemed to be independent from clinical psoriasis subtype, age at onset, gender and ethnicity. Yet the following limitations have to be considered in this context.

First, there was only one cohort including a rare psoriasis phenotype. Second, there was only one study involving Asian subjects. Third, information on mean age at onset and gender was not available for all samples. Lastly, the validity of the meta-analysis is limited by the small sample sizes of some cohorts which can cause over- or underestimation of the effect.

In spite of the positive outcome of the meta-analysis, HLA-Cw*0602 mapping only 85kb from HLA-B57 is currently claimed as the PSORS1 risk allele [324, 318, 130]. Nevertheless, there was some evidence for the presence of independent additional susceptibility factors in PSORS1, suggesting an involvement of HLA-B57 [132]. Functionally, both human leukocyte antigens are thought to play a similar role in the T cell response binding peptide motives [221].

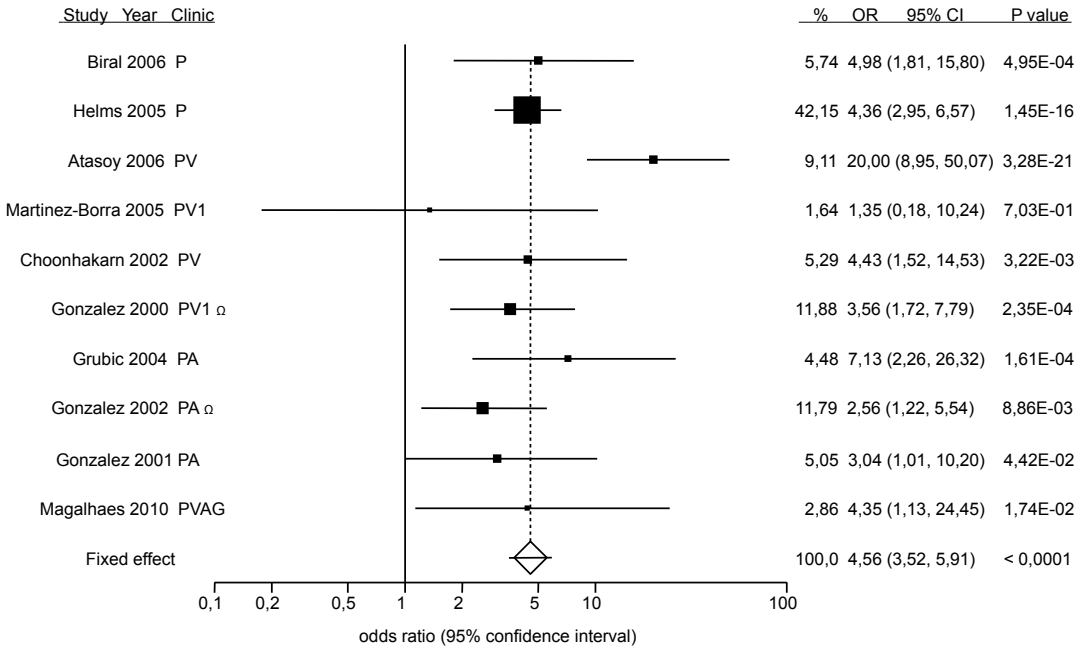


Figure 4.68.: Association of HLA-B57 with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.22.

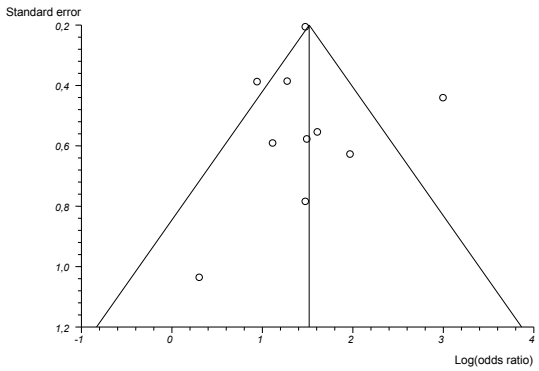


Figure 4.69.: Funnel plot showing log(OR)s and standard errors for the association of HLA-B57 with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.9644.

4.2.17. HLA-C allele Cw*0602

Like the other HLA genes, HLA-C forms part of the major histocompatibility complex within PSORS1 on chromosome 6q21.3. This highly polymorphic gene has been tested for association with psoriasis in many candidate gene studies, especially risk alleles HLA-Cw*1, *5, *7, *12 and *0602 showed positive results in at least one published study (Table 4.1, p. 56).

An association between the antigen corresponding to HLA-Cw*0602 and psoriasis had already been described by Ozawa et al 1988 [361]. Further association studies confirmed this fining, accumulating sufficient case-control data to perform a comprehensive meta-analysis.

Studies excluded from the meta-analysis. Besides Ozawa et al 1988 [361], two additional studies tested the relation between HLA-Cw antigens and psoriasis. They searched the gene products by specific antibodies. Hohler et al 1996 [191] found a significantly increased antigen frequency in German patients with psoriasis but not in those suffering from psoriatic arthritis. Oka et al 1999 [352] replicated the finding in a Japanese psoriasis cohort.

In addition, a total of eight family studies investigated the transmission of the HLA-Cw6 risk allele (Table 4.24). The said family samples comprise sets from different ethnicities like Europe, North America, India and China. Besides five panels with psoriasis vulgaris, three mixed samples including psoriatic arthritis and guttate psoriasis were identified. Relating to different onset-types, one study involved exclusively early-onset subjects while another involved late-onset subjects only. Merely the first and at the same time smallest study by Jenisch et al 1999 [220] was not able the yield a significant result in the TDT analysis.

A number of case-control studies had to be excluded due to quite different reasons. For example, Orru et al 2005 [357] tested a haplotype including HLA-Cw6 for association with psoriasis, but not the polymorphism alone. In contrast, the study by O'Brien et al 2001 [349] did not meet the quality criteria involving merely 42 cases and 38 controls. Still, it proposed an association between HLA-Cw6 and psoriasis showing a significant result. Martinez-Borra et al 2003 [304] used the same psoriasis sample set as Gonzalez et al 2000 [152]. Consequently, only the latter was included in the meta-analysis. Yet Martinez-Borra et al 2003 [304] investigated an additional psoriatic arthritis cohort.

In Ameen et al 2005 [8] the minor allele frequency of the Japanese control population did not reach the required minimum of 1%. As the allele frequency was similarly low in the Japaneses cases (4.7%), no significant difference was observed. Chang et al used HLA-Cw6 as reference in order to evaluate other associations. Consequently there were a number of similar reports in overlapping sample sets [82, 83, 81, 80, 76, 77]. The inclusion of all reports would have caused bias to the meta-analysis. Consequently, only the first in 2003 [82] and the last publication in 2007 [77] were included.

Studies included in the meta-analysis. The meta-analysis involved 44 studies comprising 48 cohorts with 10124 cases and 10845 controls. For each study the leading

Table 4.24.: Characteristics of family studies on HLA-Cw*0602 polymorphism in psoriasis

Study [Ref]	Country	Clinic	Families	Association
Fan 2008 [130]	China	PVG	163	Yes
Nair 2006 [324]	Europe	PVAG	678	Yes
Helms 2005 [177]	Europe	PVA	242	Yes
Ameen 2005 [8]	United Kingdom	PV2	153	Yes
Asumalahti 2002 [19]	Europe, India	PV (mostly)	419	Yes
Schmitt-Egenolf 2001 [422]	Germany	PV1	52	Yes
Enerback 2000 [123]	Sweden	PV	232	Yes
Jenisch 1999 [220]	US, Germany	PV	13	No

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside; Families, number of families included; Association, stating if an association was detected or not; PV, psoriasis vulgaris; PV1, early-onset psoriasis vulgaris (Type 1); PV2, late-onset psoriasis vulgaris (Type 2); PVG, psoriasis vulgaris and guttate psoriasis; PVAG, psoriasis vulgaris, psoriatic arthritis and guttate psoriasis; PVA, psoriasis vulgaris and psoriatic arthritis;

author, year of publication, country, clinical psoriasis variant, number of patients and controls, allele frequencies, mean age at onset and percentage of male patients are reported in Table 4.25.

There were sample sets from a variety of different countries and ethnicities. Most of them resided in Europe, Canada or North America and another large part descended from Asian ancestors. In addition, two cohorts were from Brazil, two from Israel and two from Australia. Relating to gender, the distribution of male patients in the different study samples ranged from 17.9% to 91.2%.

Concerning clinical phenotypes, a number of different psoriasis variants were analysed. Psoriasis vulgaris being the most common variant, was investigated most frequently and psoriatic arthritis nearly as frequently. Furthermore, there were samples without specification of the clinical psoriasis variant, mixed samples and samples with rare phenotypes including guttate psoriasis and palmoplantar pustulosis.

Around half of the studies provided detailed information on the division into early- and late-onset psoriasis. Some investigated one type only and seven studies allowed a direct comparison of the two onset-types.

Results of the meta-analysis. The overall meta-analysis yielded a highly significant result (OR = 4.73, 95%CI = 3.90-5.75, P < 0.0001) (Figure 4.70). A random effects model was applied as there was a high between-study heterogeneity with odds ratios ranging from 1.38 to 30.77 (Inconsistency: $I^2 = 90.1\%$, Chochran Q test: P < 0.0001). There was no evidence of association bias, neither in funnel plot analysis (Figure 4.71) nor in Egger's regression test (P = 0.1689).

Stratification by clinical subtype indicated significant associations regardless of joint involvement. Yet the overall association estimate was higher for the psoriasis vulgaris subgroup.

Table 4.25.: Characteristics of studies included in meta-analysis of HLA-Cw*0602 polymorphism in psoriasis

			Numbers		Freq			
Study [Ref]	**Country**	**Clinic***	**P**	**C**	**P**	**C**	**Onset**	**Male**
Liao 2008 [284]	Taiwan (A)	P	80	75	32.5	6.7	23.7 (9.0)	61.3
Biral 2006 [40]	Brazil	P (76%)	92	160	21.7	5.0	$\leq 40 \leq$	44.6
Korendowych 2006 [253] $^{\Psi 1}$	Australia	P1	49	148	67.0	18.0	-	-
Helms 2005 [177] ^{cau}	US (E)	P	436	460	31.0	8.0	23.0	-
Holm 2003 [194] $^{\Psi 2}$	Sweden (E)	P	87	50	48.0	10.0	27 (1-72)	51.7
Asumalahti 2002 [19]	Japan (A)	P $^{\#1}$	83	70	9.6	1.4	36 (1-65)	68.7
Choi 2000 [93]	Korea (A)	P (72%)	138	126	74.6	8.7	$\leq 40 \leq$	52.2
Rebala 2009 [390]	Poland (E)	PV2	383	143	18.8	12.6	≥ 30	-
Szczerkowska-D. 2007 [461]	Poland (E)	PV2	89	80	14.6	9.4	≥ 40	39.3
Chang 2007 [77] $^{\Phi 1 \Psi 3}$	Taiwan (A)	PV (49%)	170	210	17.4	4.8	$\leq 40 \leq$	72.4
Atasoy 2006 [20]	Turkey (E)	PV (69%)	72	104	66.0	8.6	-	59.7
Martinez-B. 2005 [303]	Israel	PV1	59	79	19.5	12.0	27.4 (13.9)	66.1
Holm 2005 [195] $^{\Psi 2}$	Sweden (E)	PV (most)	218	110	59.0	12.0	20 (1-72)	52.4
Allen 2005 [6]	UK (E)	PV2	145	308	15.0	8.1	≥ 40	-
Luszczek 2004 [292]	Poland (E)	PV (87%)	116	123	77.2	17.1	23.7 (15.2)	56.9
Sanchez 2004 [418]	Sweden (E)	PV1	98	120	62.2	10.8	(<1-25)	50.0
Chang 2003 [82] $^{\Psi 3}$	Taiwan (A)	PV (53%)	105	160	18.6	6.6	$\leq 40 \leq$	75.2
Orru 2002 [358]	Italy (E)	PV	147	120	28.0	17.5	31.7 (19.1)	57.1
Tsai 2002 [482]	Taiwan (A)	PV (66%)	68	213	16.2	5.2	(12-78)	72.1
Choonhakarn 2002 [94]	Thai (A)	PV	140	300	14.0	3.0	-	-
Gonzalez 2000 [152] $^{\Phi 2}$	Spain (E)	PV1	95	104	49.4	21.1	26.9 (15.1)	41.1
Tazi Ahnini 1999 [472]	UK (E)	PV	235	374	36.0	10.0	-	48.9
Gonzalez 1999 [154] $^{\Phi 3}$	Spain (E)	PV	45	177	57.7	18.0	-	55.6
Mallon 1997	UK (E)	PV	87	604	47.1	20.2	$\leq 40 \leq$	57.5
Fojtikova 2009 [137]	CR (E)	PA (67%)	100	94	36.0	15.9	$\leq 40 \leq$	49.0
Liao 2008 [284]	Taiwan (A)	PA	91	75	16.5	6.7	37.0 (11.6)	55.0
Chang 2007 [77] $^{\Phi 1}$	Taiwan (A)	PA (74%)	102	210	7.4	4.8	$\leq 40 \leq$	52.0
Suomela 2007 [459] $^{\Phi 4}$	Finland (E)	PA	66	93	35.6	9.0	24 (1-40)	66.7
Korendowych 2006 [253] $^{\Psi 1}$	Australia	PA	158	148	43.0	18.0	-	-
Szczerkowska-D. 2005 [462]	Poland (E)	PA	41	80	56.0	18.7	-	61.0
Grubic 2004 [160]	Croatia (E)	PA	58	157	16.4	9.6	33.8 (19-54)	48.3
Martinez-B. 2003 [304] $^{\Phi 2}$	Spain (E)	PA1	74	104	62.0	21.1	23 (9)	-
Martin 2002 [302]	Canada (E)	PA	366	299	16.3	9.5	-	-
Gonzalez 2002 [153] $^{\Psi 4}$	Spain (E)	PA	81	110	60.0	17.0	31 (11)	60.5
Al-Heresh 2002 [3]	UK (E)	PA	124	101	41.0	26.0	$\leq 40 \leq$	48.4
Gonzalez 2001 [151]	Israel	PA	52	73	28.8	21.9	36.4 (15.7)	-
Gonzalez 1999 [154] $^{\Phi 3 \Psi 4}$	Spain (E)	PA	65	177	58.4	18.0	29 (11.5)	56.9
Magalhaes 2010 [297]	Brazil	PVAG	69	70	26.1	10.0	-	-
Stuart-1 2010 [456]	US (E)	PVAG	2438	2311	23.4	9.1	-	30.4
Stuart-2 2010 [456]	Thai (A)	PVAG	206	114	17.7	4.3	34.0 (1.1)	-
Feng 2009 [132]	US (E)	PPA (83%) $^{\#2}$	1359	1400	47.0	16.0	24.3	48.3
Sanchez 2008 [419]	Sweden (E)	PPA (49%)	645	472	38.6	11.1	(12-84)	91.2
Brazzelli 2000 [50]	Italy (E)	PPA $^{\#3}$	40	122	25.0	8.6	$\leq 40 \leq$	75.0
Suomela 2007 [459] $^{\Phi 4}$	Finland (E)	PVGPPP	309	93	57.4	9.0	20 (0-40)	56.0
Asumalahti 2000 [17] $^{\Phi 4}$	Finland (E)	PVGI	100	93	37.0	9.0	(3-80)	-
Asumalahti 2003 [16] $^{\Phi 5}$	UK (E)	PPP $^{\#4}$	106	309	20.0	15.0	51	17.9
Asumalahti 2003 [16] $^{\Phi 5}$	UK (E)	PG $^{\#5}$	134	309	83.0	15.0	17.5	45.0
Tazi Ahnini 1999 [473]	UK (E)	PG	103	501	-	-	-	-
Total			10124	10845	37.3	11.7		

(Continued)

(Continued)

Study, given by first author and year of publication; Ref, reference; Country, where the subjects reside and their descent in brackets; E, European; A, Asian; Numbers, numbers of patients and controls; P, patients; C, controls; Freq, frequency of the HLA-Cw*0602 allele in %; Clinic, clinical psoriasis variant/s; *, percentage of early-onset psoriasis (Type 1) in brackets; Onset, mean age at onset with standard deviation or range in brackets; $\leq 40 \leq$, patients with onset before and after 40 years (early- and late-onset psoriasis) involved; Male, percentage of male patients in %; CR, Czech Republic; P, psoriasis without further specification; P1, early-onset psoriasis (Type 1); PV, psoriasis vulgaris; PV1, early-onset psoriasis vulgaris (Type 1); PV2, late-onset psoriasis vulgaris (Type 2); PA, psoriatic arthritis; PA1, early-onset psoriatic arthritis (Type 1); PG, guttate psoriasis; PPP, palmoplantar pustulosis; PI, inverse psoriasis; PVAG, psoriasis vulgaris, psoriatic arthritis and guttate psoriasis; PVGPPP, psoriasis vulgaris, guttate psoriasis and palmoplantar pustulosis; PVGI, psoriasis vulgaris, guttate psoriasis and inverse psoriasis; PPA, psoriasis without further specification and psoriatic arthritis; ^{cau}, the control group named *CAU* was used for the meta-analysis; $^{\Phi 1-5}$, these studies use the same control subjects, respectively; $^{\Psi 1-4}$, these studies may show an overlap of study populations, respectively; $^{\#1}$, 52% PV; $^{\#2}$, 27.1% PA; $^{\#3}$, 22.5% PA; $^{\#4}$, 18% PPP and PV; $^{\#5}$, 56% guttate flare of PV; - , data not provided in the article;

- Psoriasis vulgaris: OR = 4.43, 95%CI = 3.06-6.43, P < 0.0001; Fig. 4.72, 4.73
- Psoriatic arthritis: OR = 3.26, 95%CI = 2.36-4.49, P < 0.0001; Fig. 4.74, 4.75

In addition, the two publications addressing the risk conceded by guttate psoriasis obtained higher odds ratios than most other studies. Yet the high association estimate may be caused by low mean age at onset (17.5 years) rather than clinical subtype in the investigation of Asumalahti et al 2003 [16]. As the second study on guttate psoriasis by Tazi Ahnini et al 1999 [473] did not provide mean age at onset nor distribution of early- and late-onset types, the hypothesis could not be validated.

Palmoplantar pustulosis, however, seemed not to be related to the polymorphism as the original study by Asumalahti et al 2003 [16] did not yield a significant result. Still, characteristics like high mean age at onset (51 years) and/or low percentage of male subjects (17.9%) could be relevant as possible disturbance factors.

As mentioned, seven studies analysed early- and late-onset psoriasis patients separately. A meta-analysis of the early-onset subsets yielded a highly significant association estimate, while the late-onset subset achieved a considerably lower pooled odds ratio.

- Early-onset: OR = 11.04, 95%CI = 5.07-24.02, P < 0.0001; Fig. 4.76a, 4.77a
- Late-onset: OR = 2.14, 95%CI = 1.51-3.03, P < 0.0001; Fig. 4.76b, 4.77b

Eight more studies investigated early- or late-onset patients only, confirming the hypothesis of an onset-type dependent association. The association estimates of five early-onset cohorts were highly significant while the three late-onset cohorts remained beneath the significance level of 0.05%. As a consequence, the low mean age at onset could have influenced the highly positive result of Asumalahti et al 2003 [16] as well.

After stratification by ethnic group, separate meta-analyses indicated that the HLA-Cw6 allele was significantly associated with psoriasis in both European and Asian populations. While the original studies involving Brazilian and Australian patients showed

significant results as well, there seemed be a different mode of inheritance in Israeli populations.

- Europe: OR = 4.56, 95%CI = 2.88-7.23, P < 0.0001; Fig. 4.78a, 4.79a
- Asia: OR = 4.03, 95%CI = 2.97-5.48, P < 0.0001; Fig. 4.78b, 4.79b

Allele frequencies in control populations ranged from 1.4% to 26.0%, resulting in an average of 11.7%. When considering different ethnicities, the allele seemed to be less frequent in Japans (1.4%), Thais (4.3%) and Latin Americans from Brazil (7.5%), and more frequent in Israeli (17.0%) and Australians (18.0%). All European control populations taken together made up a mean frequency of 13.6%, while Asian control populations showed a considerably lower frequency of 5.1%.

Discussion of the meta-analysis. The present meta-analysis showed that the HLA-Cw*0602 allele is a significant risk factor for psoriasis. Yet the association seemed to be dependent on some characteristics of the samples. Concerning psoriasis subtypes, a comparison of cohorts with and without joint involvement showed a stronger effect for those without additional arthritis. This tendency was seen in an excluded study by Hohler et al 1996 [191] as well. They had found a significantly increased antigen frequency in German patients with psoriasis, but not in those suffering from psoriatic arthritis. Relating to rare phenotypes, there were highly significant association estimates for guttate psoriasis, but a negative report for palmoplantar pustulosis.

Age at onset seemed to have great influence as well. The meta-analysis of early-onset cohorts demonstrated a considerably higher association estimate than for the respective late-onset cohorts. Concerning ethnicity, HLA-Cw*0602 was associated with both European and Asian populations, yet demonstrating a lower allele frequency in the latter. Most excluded studies replicated this finding. Only a German family study by Jenisch et al 1999 [220] and a Japanese case-control study by Ameen et al 2005 [8] did not reach statistical significance. Two studies on Israeli populations, however, indicated an absence of association in this country. There seemed not to be a dependency on gender.

Yet some limitations of the meta-analysis have to be taken into account. First, studies with small samples sizes might have over- or underestimated the effect. Second, unspecified and mixed cohorts impeded a comprehensive assessment of dependency from clinical subtype. Third, data on the distribution of onset-types was limited. Forth, the predominantly investigated ethnicities were European and Asian.

In summary, the meta-analysis demonstrated an association of HLA-Cw*0602 with psoriasis, especially in early-onset psoriasis vulgaris and guttate psoriasis from European and Asian populations. The high association estimate of 4.73 and the small confidence interval supports the status of HLA-C as the major risk gene in PSORS1 and for psoriasis in general [324, 318, 130]. Still, there is some evidence for additional risk factors within the major histocompatibility complex as well [132]. Functionally, HLA-C as a MHC class I molecule is thought to play an important role in the T cell function binding peptide motives [221].

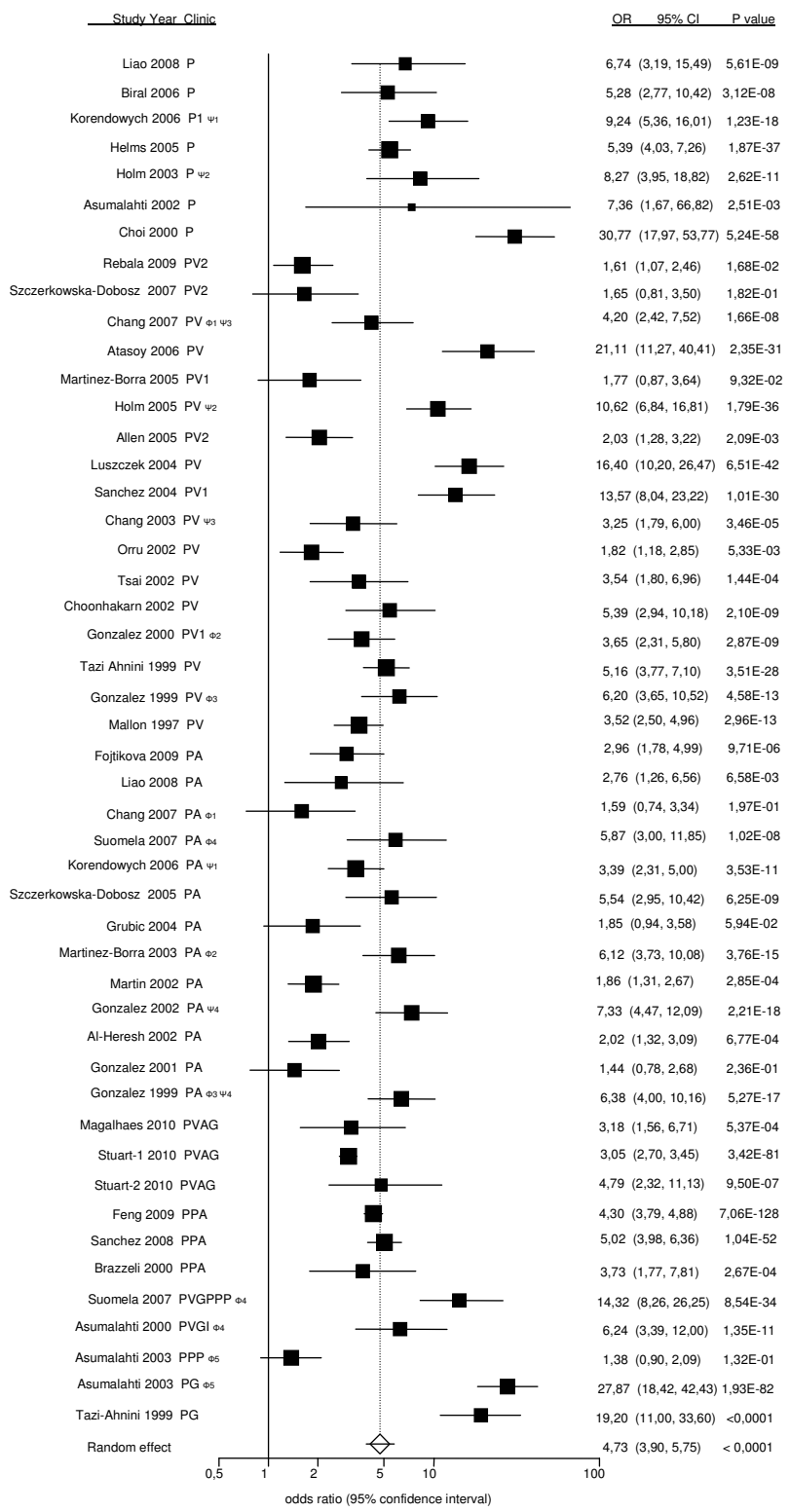


Figure 4.70.: Association of HLA-Cw6 with psoriasis. Forest plot showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analysis. %, weight; abbreviations see Table 4.25.

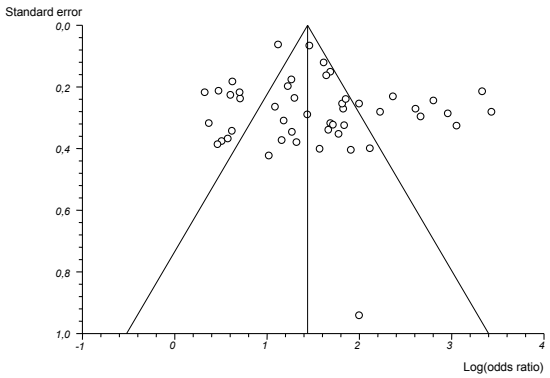


Figure 4.71.: Funnel plot showing log(OR)s and standard errors for the association of HLA-Cw6 with psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.1689.

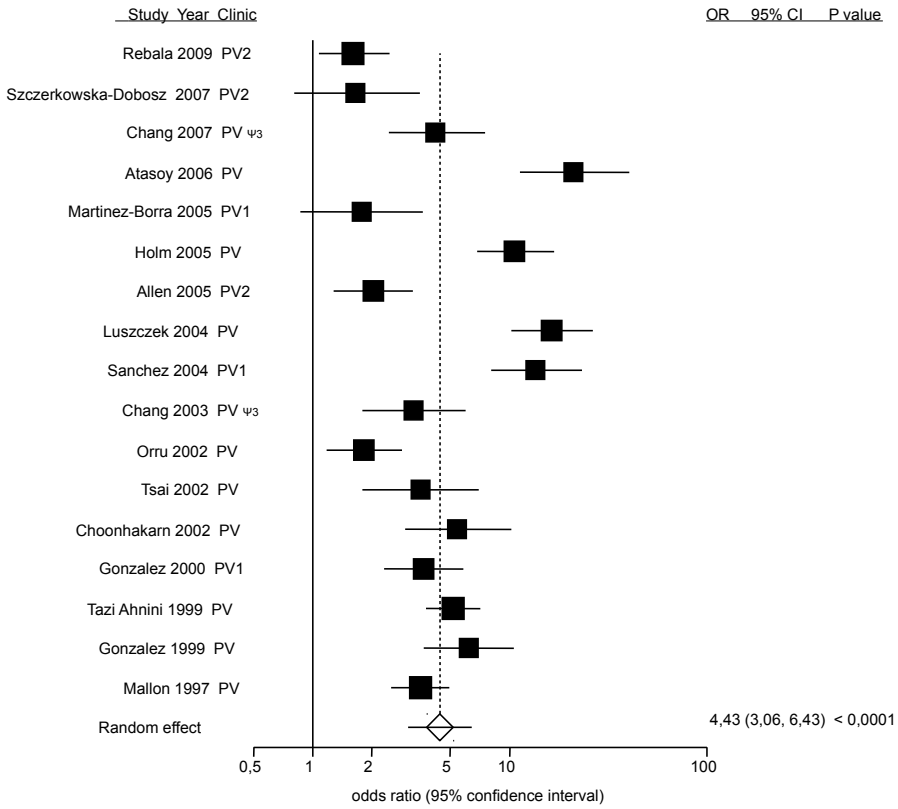


Figure 4.72.: Association of HLA-Cw6 with psoriasis vulgaris. Forest plots showing ORs and 95% CIs for the studies (given by first author, year and country) included in the meta-analyses. Abbreviations see Table 4.25.

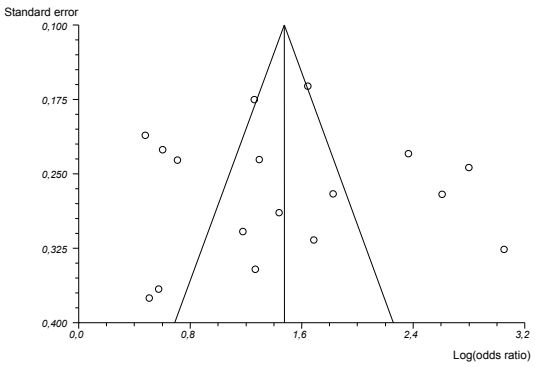


Figure 4.73.: Funnel plots showing log(OR)s and standard errors for the association of HLA-Cw6 with psoriasis vulgaris. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.8359.

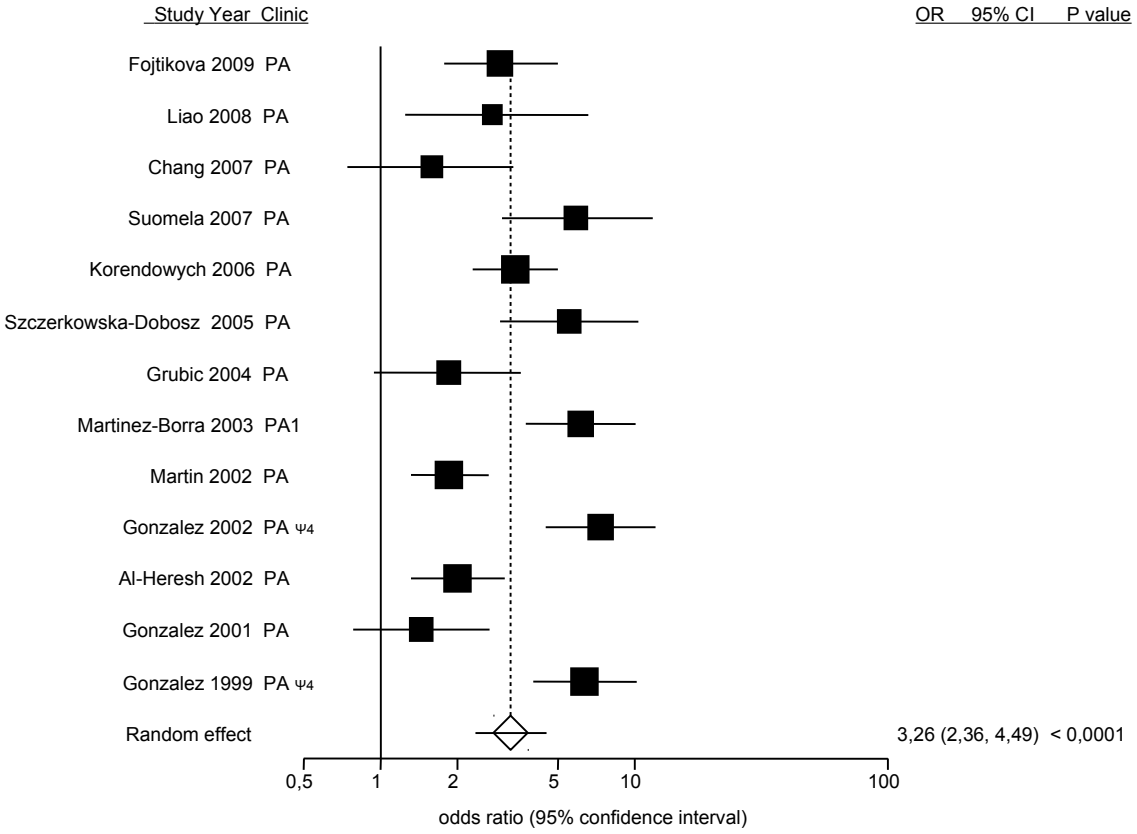


Figure 4.74.: Association of HLA-Cw6 with psoriatic arthritis. Forest plots showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analyses. Abbreviations see Table 4.25.

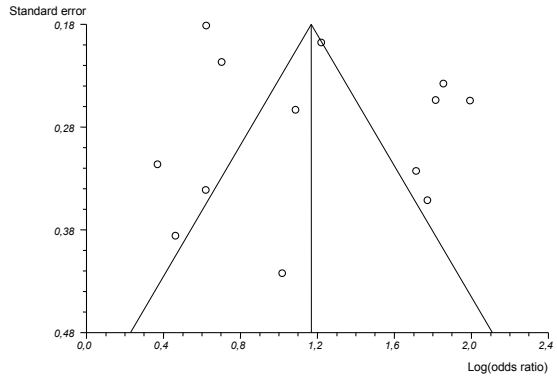
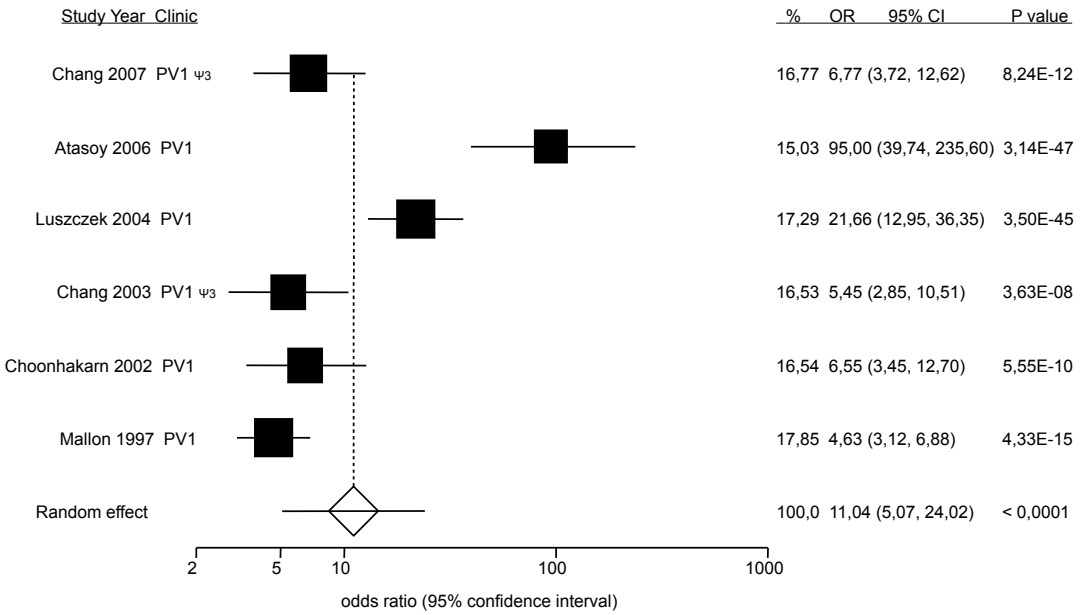
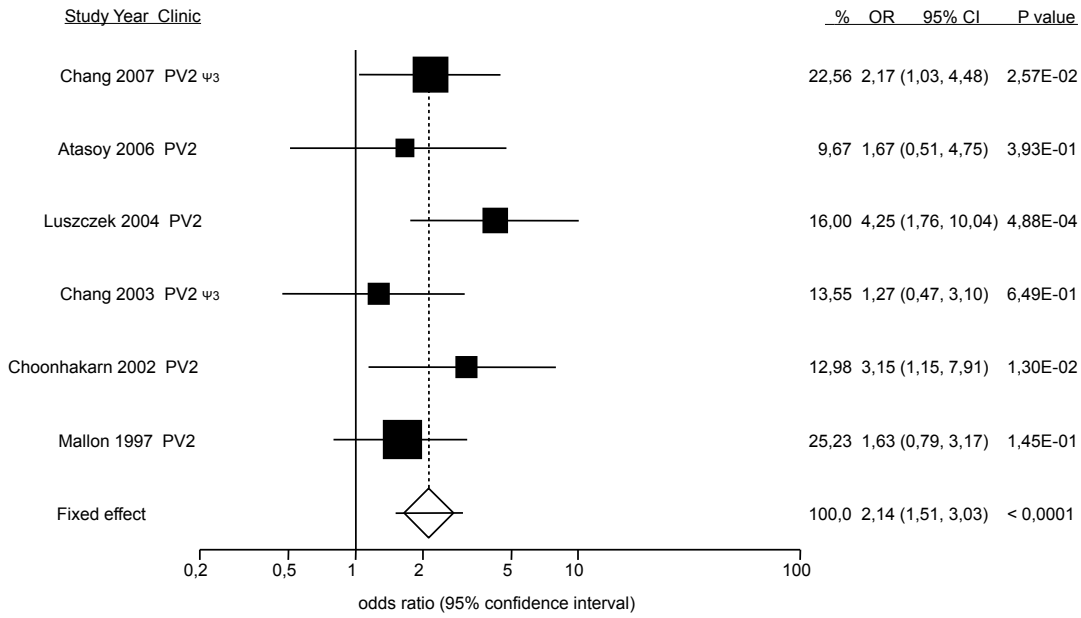


Figure 4.75.: Funnel plots showing log(OR)s and standard errors for the association of HLA-Cw6 with psoriatic arthritis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P = 0.8235.

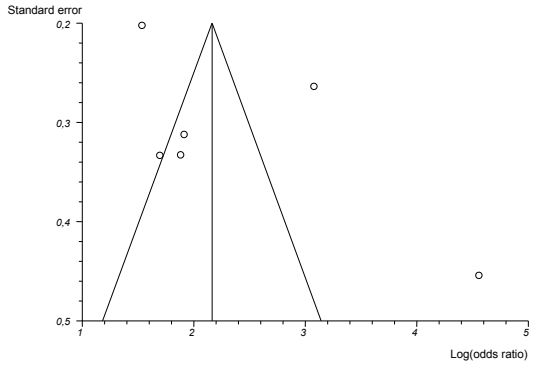


(a) Early-onset

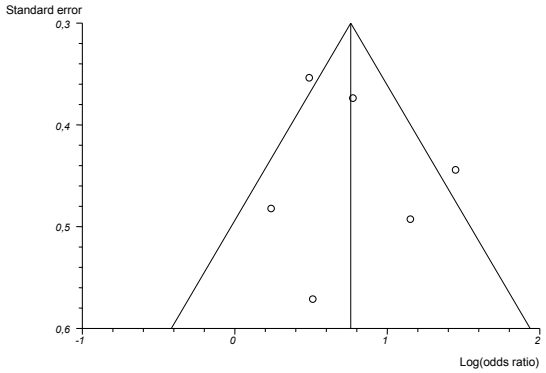


(b) Late-onset

Figure 4.76.: Association of HLA-Cw6 with (a) early-onset and (b) late-onset psoriasis. Forest plots showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analyses. Abbreviations see Table 4.25.

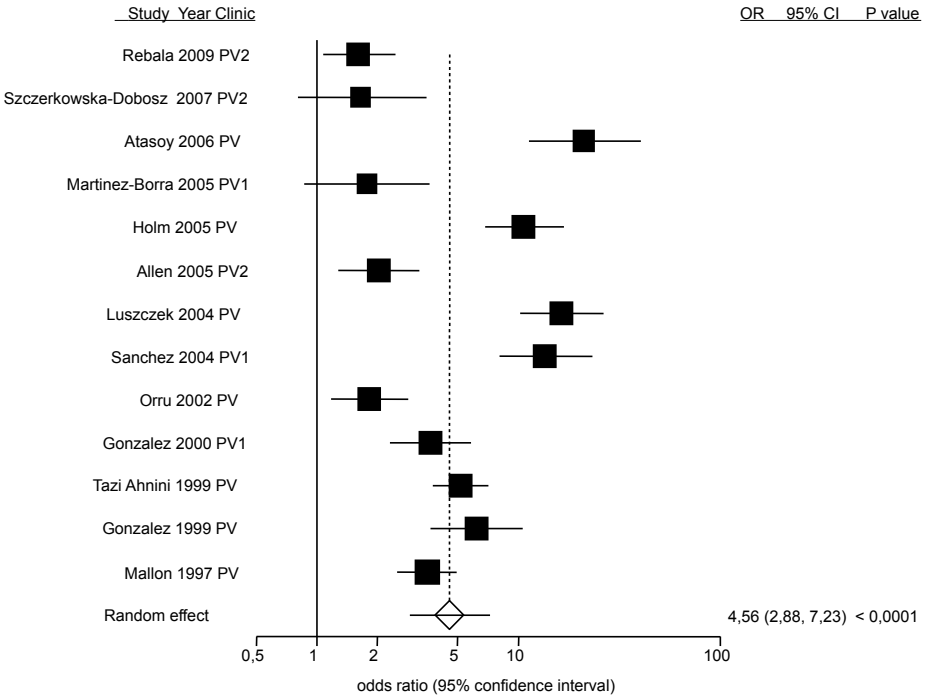


(a) Early-onset

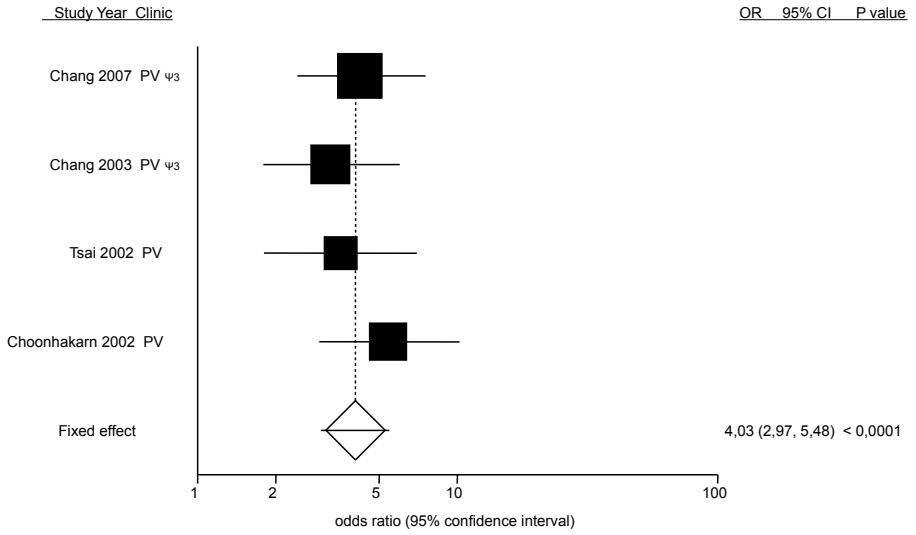


(b) Late-onset

Figure 4.77.: Funnel plots showing log(OR)s and standard errors for the association of HLA-Cw6 with (a) early-onset and (b) late-onset psoriasis. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P values > 0.05; (a) $P = 0.2205$; (b) $P = 0.8564$.

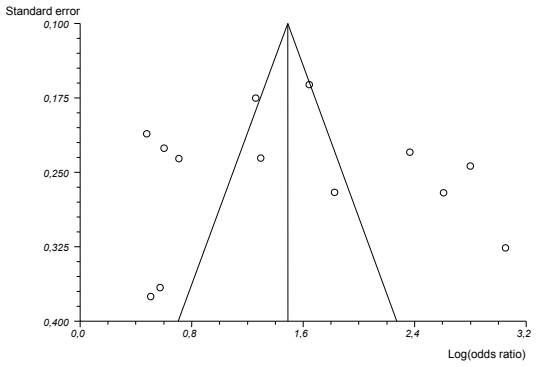


(a) Europe

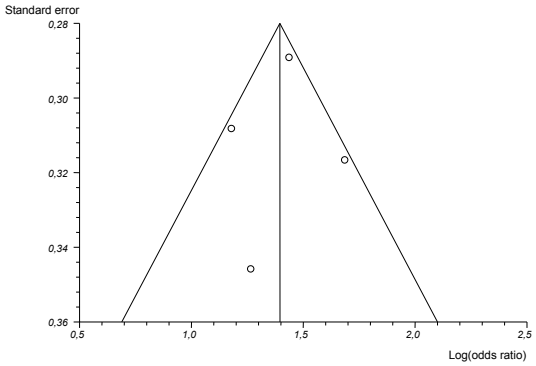


(b) Asia

Figure 4.78.: Association of HLA-Cw6 with psoriasis in (a) European and (b) Asian populations. Forest plots showing ORs and 95% CIs for the studies (given by first author, year and clinical psoriasis variant) included in the meta-analyses. Abbreviations see Table 4.25.



(a) Europe



(b) Asia

Figure 4.79.: Funnel plots showing log(OR)s and standard errors for the association of HLA-Cw6 with psoriasis in (a) European and (b) Asian populations. Bias indicators showed no significant deviation from the symmetry assumption, thus not indicating publication bias: Egger's regression test P values > 0.05; (a) $P = 0.7619$; (b) $P = 0.8345$.

4.3. Relevance of genetic predispositions to psoriasis

As seen in the previous sections, evidence levels for genetic predispositions can vary widely. They range from single positive reports through replicated reports up to multi-stage genome-wide association studies and large meta-analyses. As a consequence, the candidate genes for psoriasis can be rated according to their relevance.

Apart from 80 candidate genes with exclusively negative reports (Table B.2, p. 243), the comprehensive *MEDLINE* search identified 144 genetic predispositions which had shown association with psoriasis in at least one published study. Together with successful and unsuccessful replications, they are summed up in Table B.1 on page 235. In addition, the karyogram in Figure 4.80 provides an overview on the chromosomal locations of all candidate genes showing at least a single positive report. Yet more than half of them have not been replicated and thus might be false positive reports.

Ten of these candidate genes obtained loose replications, in other words they were associated with psoriasis in at least two independent cohorts but in deviating genetic variants. This was the case for some interleukin genes like IL20 on chromosome 1q32 and IL1B on chromosome 2q14 as well as for genes lying in psoriasis susceptibility loci like AGER, PSORS1C1, PSORS1C2 and PSORS1C3 in PSORS1 on chromosome 6p21.3, for SLC12A8 in PSORS5 on chromosome 3q21 and MMP2 in PSORS8 on chromosome 16q.

Interestingly, there was also a loose replication for FLG in the epidermal differentiation complex (EDC) on chromosome 1q21 which is the major atopic eczema risk gene. Yet variants associated with psoriasis differed form those associated with atopic eczema. All of the listed loose replications were reported in high-quality studies with an appropriate sample size of at least 100 subjects.

Further 55 candidate genes showed strict replications, in other words they were associated with psoriasis in at least two independent cohorts and in the same genetic variant. All were replicated in studies which met some quality criteria as mentioned above (Table B.1, p. 235). The locations of these genetic predispositions with strict replications are visualized and labeled in Figure 4.81.

In total, 27 of them have been discovered and replicated in sample sets of genome-wide association studies, reaching a higher level of evidence due to large sample sizes and a hypothesis-free approach. For example, ERAP1 on chromosome 5q15 as well as genes involved in NF-κB signaling like TNIP1 on chromosome 5q32-q33.1, TNFAIP3 on chromosome 6q23, TRAF3IP2 on chromosome 6q21 and NFKBIA on chromosome 14q13 and genes involved in IFN-signaling like IFIH1 on chromosome 2q24 were even replicated in independent genome-wide scans. All genetic predispositions affirmed by genome-wide association studies (GWAS) are indicated with an asterisk in Figure 3.9.

In addition, a number of replicated candidate genes have been investigated by meta-analyses. In this case, the weight of genetic predispositions can be assessed by the association estimates achieved in the corresponding analyses. For psoriasis, several meta-analyses could be added to the existing ones on LCE3C_LCE3B deletion and VEGFA variant +405G while meta-analyses on TNF variants -308A and -238A were extended by further case-control studies.

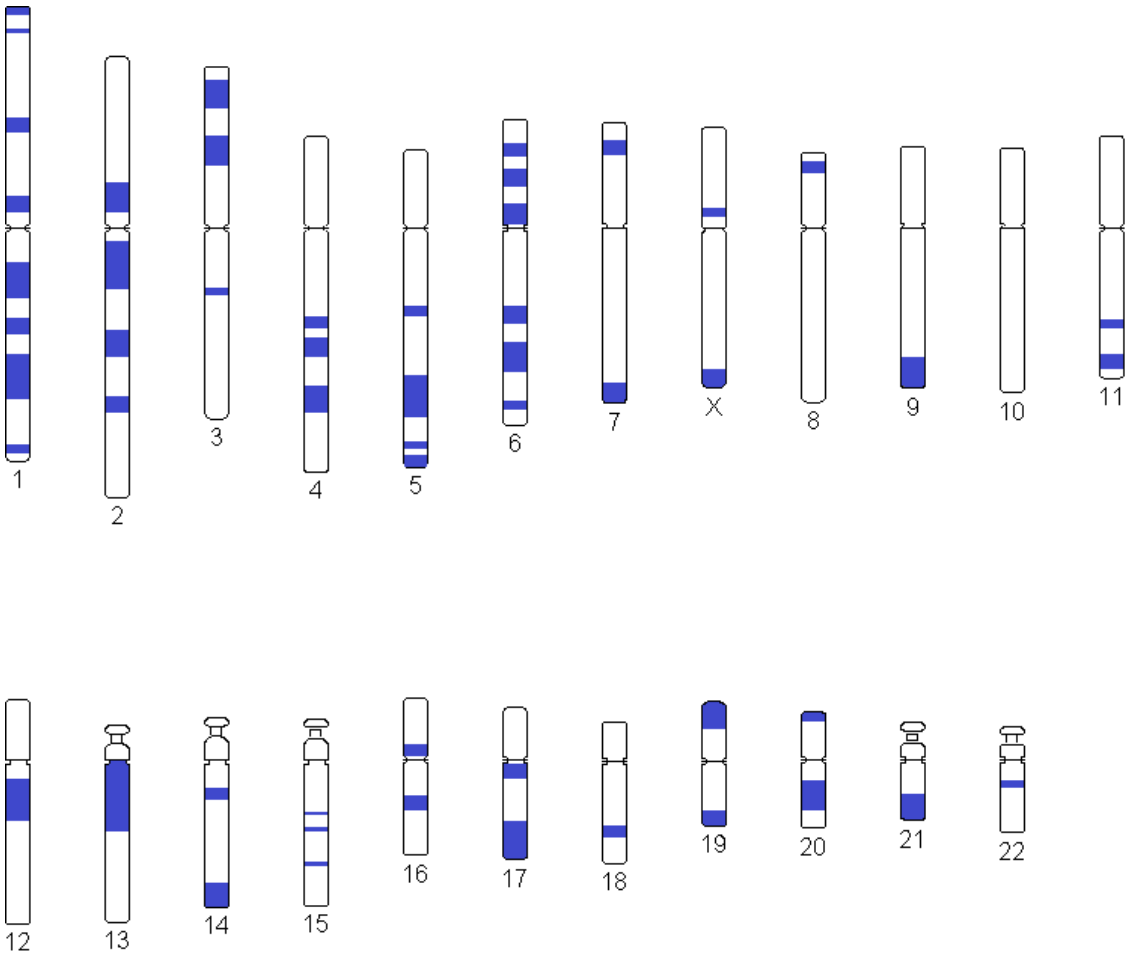


Figure 4.80.: Karyogram showing locations of genes with at least one positive report for psoriasis.

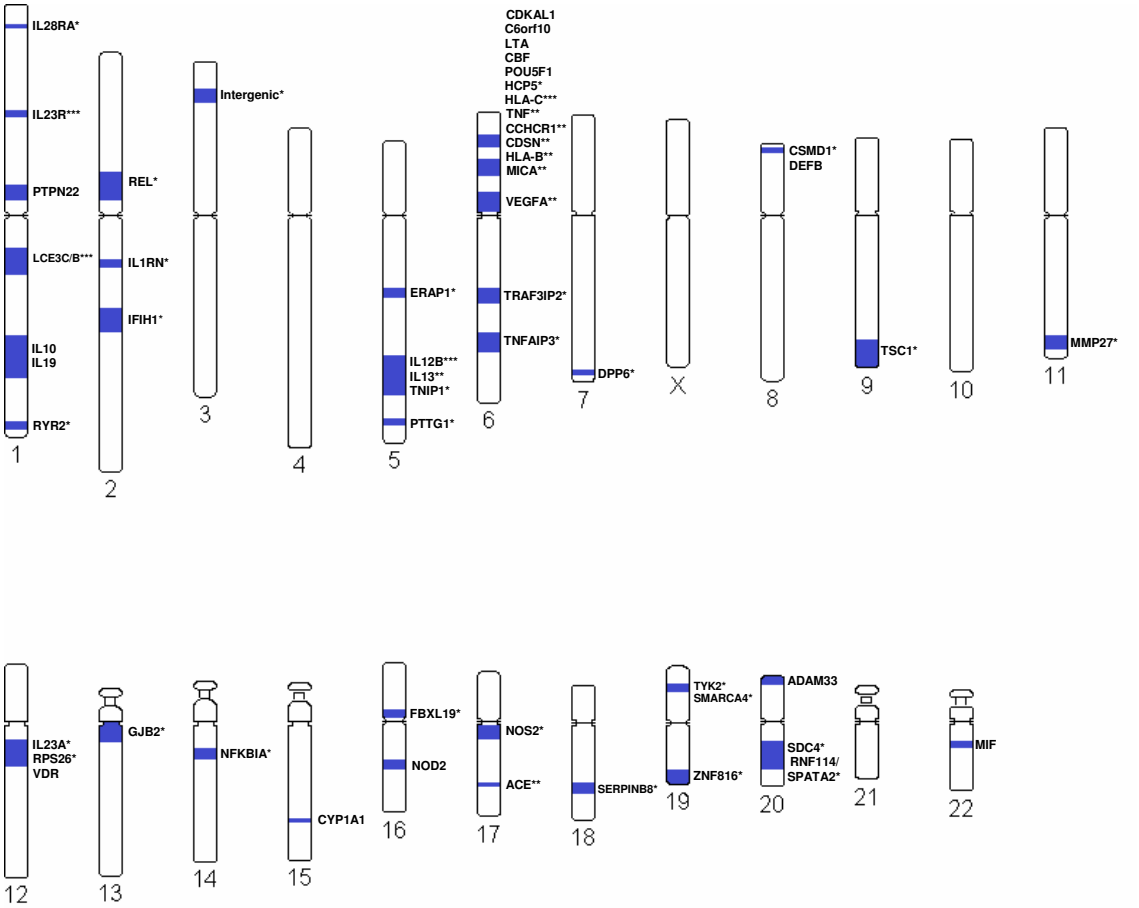


Figure 4.81.: Karyogram showing locations of genes with strict replications in high-quality studies for psoriasis: *, affirmed by GWAS, **, affirmed by meta-analysis, ***, affirmed by both meta-analysis and GWAS.

In Figure 4.82, association estimates of all meta-analyses are compared to each other. As can be seen, a total of four meta-analyses did not reach statistical significance involving the investigations on IL1RN variable number tandem repeat, IL10 variant -1082G, PTPN22 variant rs2476601 (R620W) and VDR restriction fragment length polymorphisms like TaqI.

Further genetic predispositions outside the major risk locus PSORS1 showed moderate effects ranging from 1.25 to 1.47 involving candidate genes ACE, VEGFA, LCE3C/B, IL13 and IL12B. A significant protective effect of 0.62 was observed for the IL23R rs11209026 A allele.

In addition, all genetic predispositions within PSORS1 showed highly significant results ranging from 1.51 to 4.56. Those include MICA, CDSN, TNF, SNP n.9, CCHCR1, HLA-B and HLA-C. Demonstrating the highest association estimate, the HLA-Cw*0602 allele was supported as the major psoriasis risk factor (Figure 4.82).

While most candidate genes were affirmed by meta-analyses only, HLA-C as well as LCE3C/B, IL12B and IL23R demonstrated significant associations in both genome-wide association scans and powerful meta-analyses, supporting their status as important risk genes for psoriasis. They were marked by two/three asterisks in Figure 4.81.

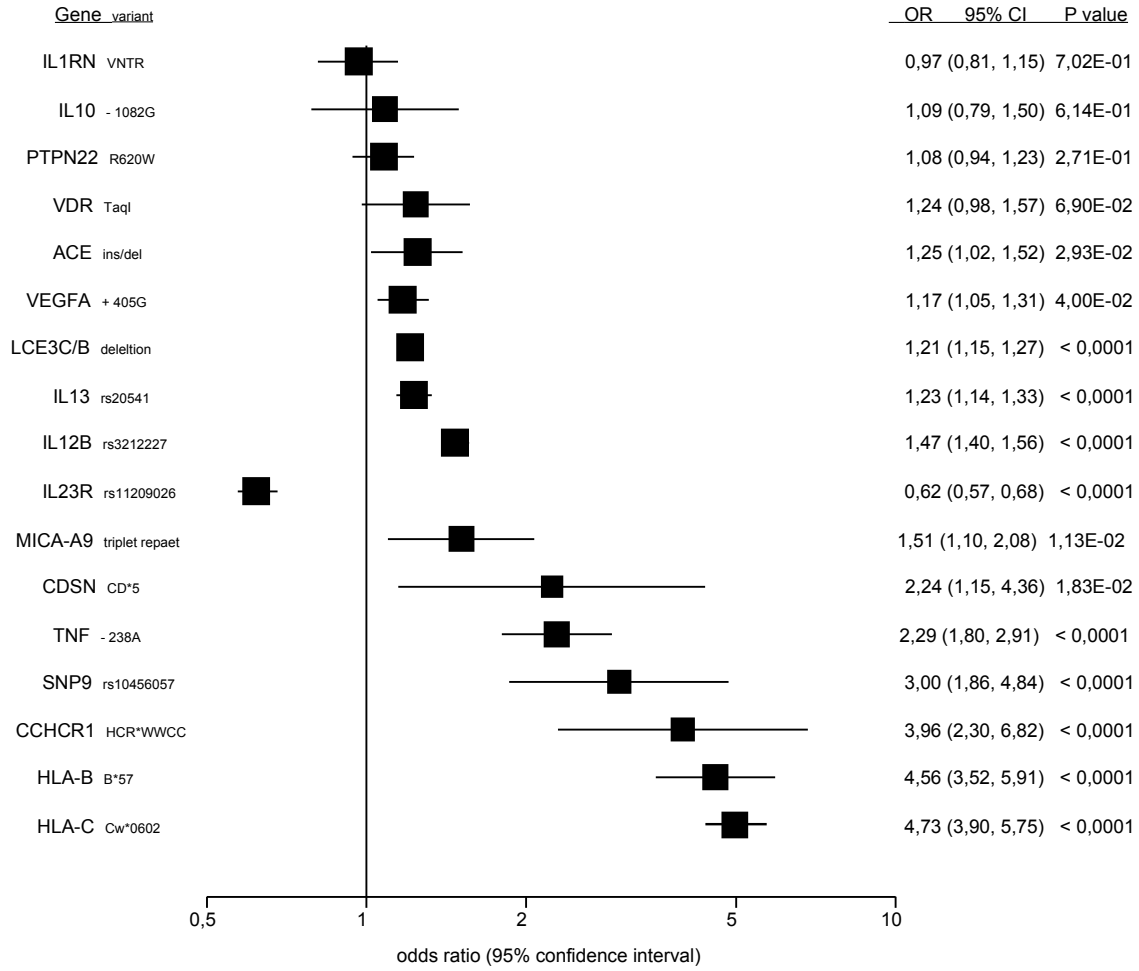


Figure 4.82.: Comparison of association estimates achieved in meta-analyses for psoriasis, given by gene and variant. If meta-analyses were performed for more than one variant per gene, the most significant was selected.

5. Comparison of genetic predispositions to atopic eczema and psoriasis

Atopic eczema and psoriasis know as complex diseases with a multifactorial genesis. As a consequence, environmental triggers contribute to their development together with multiple genes. In addition, both are classified among the chronic inflammatory skin disorders sharing clinical features like a dry, scaly skin as well as histological features like a thickening of the epidermis and an inflammatory infiltrate.

The pathogenesis of both diseases shows parallels as well, involving a dysfunction of the epidermis and a dysregulation of the immune response. Hereby, similar cell types and mediators like cytokines play an important role. Taking into account these similarities, a shared genetic background of these two chronic inflammatory skin diseases seems conceivable.

While twin studies promoted the presence of underlying heritable factors for both diseases, genetic linkage analyses showed an overlap of susceptibility loci in six chromosomal locations. In addition, some association studies happened to study divergent candidate genes in the same location or even shared candidate genes.

In contrast to these shared positive reports on genetic predispositions, there were common negative reports and contrasting reports as well. They indicated candidate genes which were either irrelevant for both diseases or only relevant for one disease. According to this, genetic predispositions to atopic eczema and psoriasis shall be compared in the following.

5.1. Overlap of susceptibility loci

The question of a shared genetic background was prompted by a report on overlapping susceptibility loci for atopic eczema and psoriasis by Cookson et al 2001 [100]. They found that their peaks of linkage coincided on chromosomes 1q21, 17q25 and 20p with shared markers D1S498, D17S784 and D20S186. In addition, they observed an overlap on 3q21 where Lee et al 2000 [275] had discovered a susceptibility locus for atopic eczema earlier.

As can be seen in Figure 5.1, susceptibility loci ATOD2 and PSORS4 overlap on chromosome 1q21 containing the epidermal differentiation complex (EDC). Replicated associations with candidate genes in this region were described for both diseases.

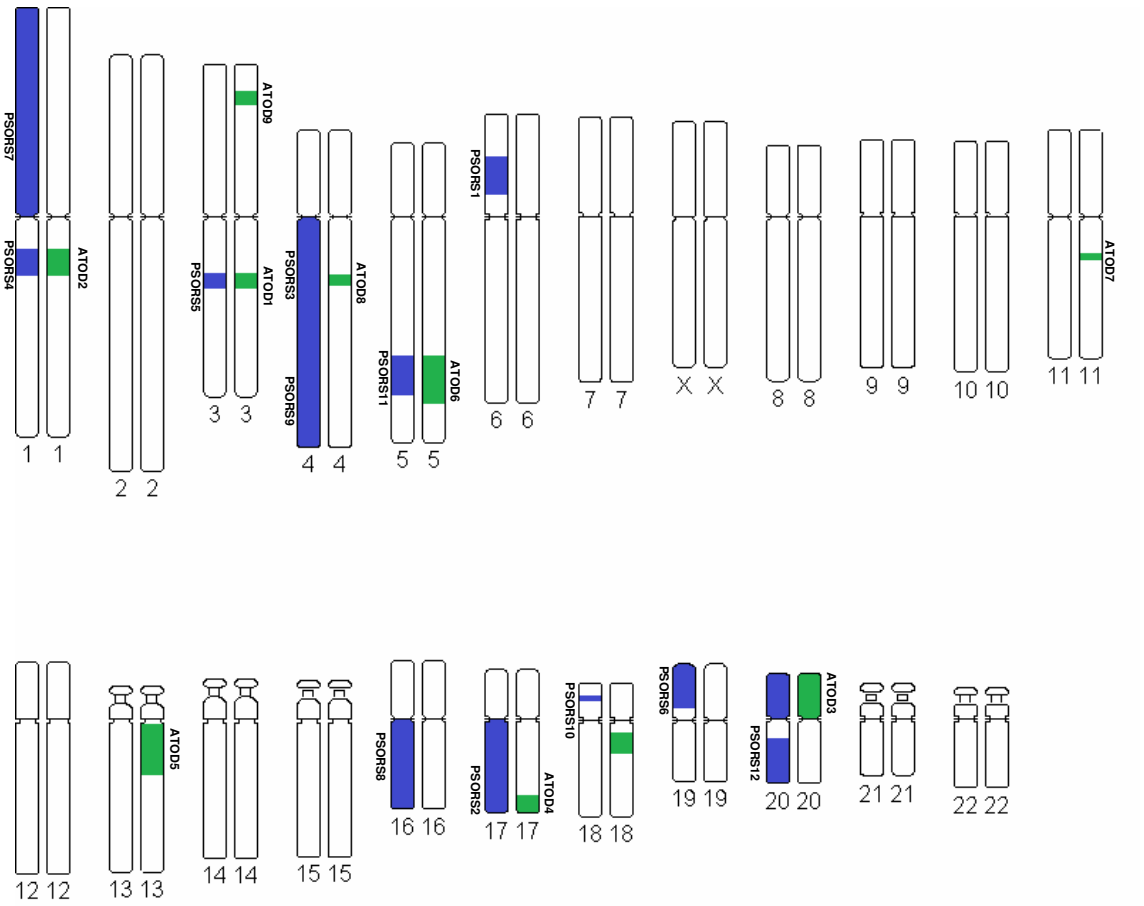


Figure 5.1.: Karyogram showing susceptibility loci for atopic eczema and psoriasis established by linkage analyses; left chromatid, PSORS1-12; right chromatid, ATOD1-9.

While ATOD4 and PSORS2 coincide on chromosome 17q25, there is an overlapping region on chromosome 20p including ATOD3. Both locations contain risk genes for both diseases validated by candidate gene studies.

On chromosome 3q21, the marker D3S3606 showed peaks of linkage for both atopic eczema (Lee 2000 [275]) and psoriasis (Enlund 1999 [125]). Here, susceptibility loci ATOD1 and PSORS5 coincide containing a number of candidate genes.

Apart from the regions published by Cookson et al, an additional overlap can be seen on chromosome 5q31.1-q33.1 where both ATOD6 and PSORS11 contain more than one promising candidate gene.

Furthermore, linkage analyses for both diseases showed associations to the q arm of chromosome 4. While for psoriasis some putative candidate genes were described in this region, for atopic eczema none was defined.

5.2. Shared positive reports on genetic predispositions

The overlap of risk loci discovered in genetic linkage analyses indicated a shared genetic background for atopic eczema and psoriasis. Each of these linkage regions, however, included a variable number of candidate genes for either one or the other or both diseases.

Further investigations on candidate genes have been carried out by association studies. They identified genetic predispositions inside and outside of established susceptibility loci. All positive reports for atopic eczema are summarized in Table A.1 on page 225 and for psoriasis in Table B.1 on page 235.

These positive reports for both diseases showed overlaps in several chromosomal locations (Figure 5.2). Yet many of these reports on putative genetic predispositions have not been replicated and might be false positive reports. Thus, the impression that almost every chromosome carries risk genes for atopic eczema and psoriasis might be misleading.

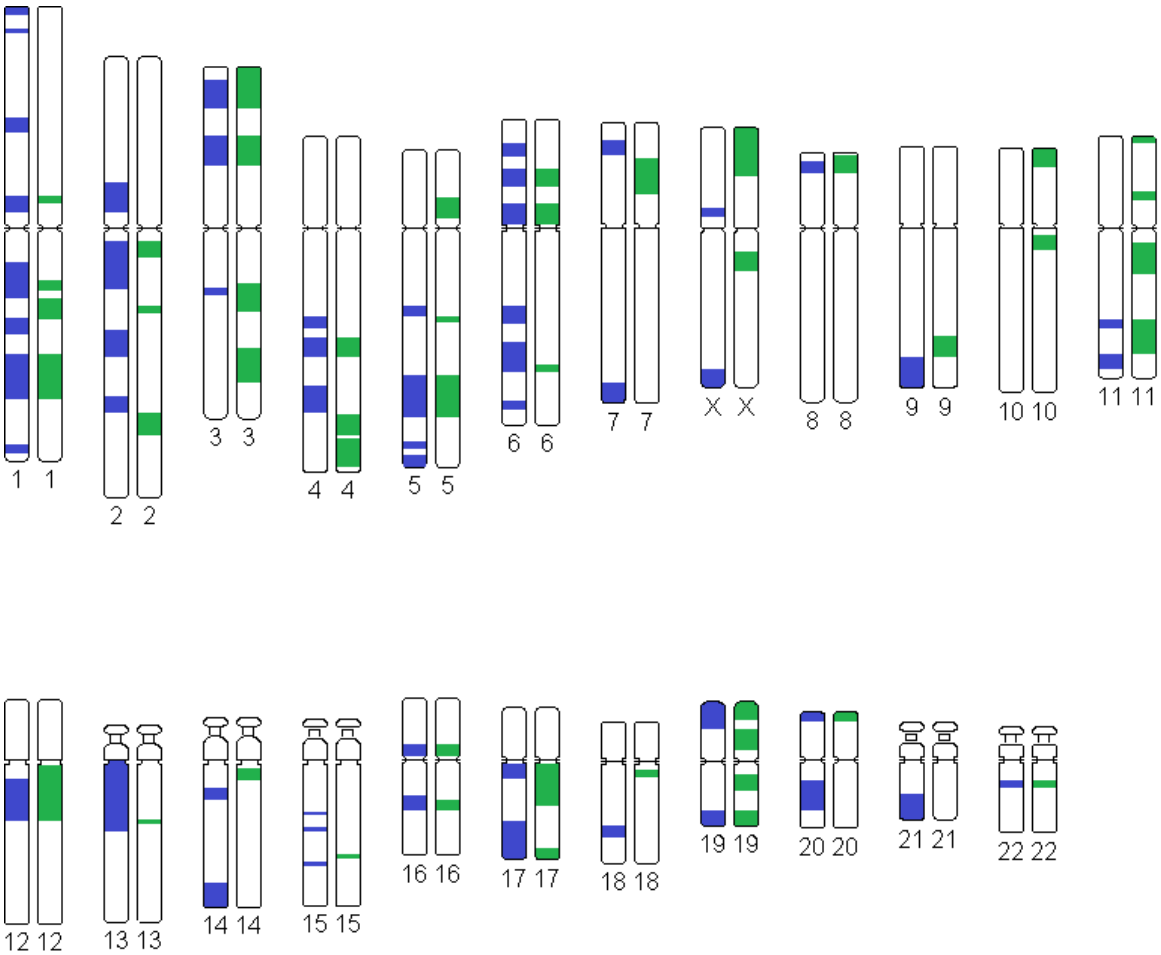


Figure 5.2.: Karyogram showing locations of genes with at least one positive report for both diseases; left chromatid, psoriasis; right chromatid, atopic eczema.

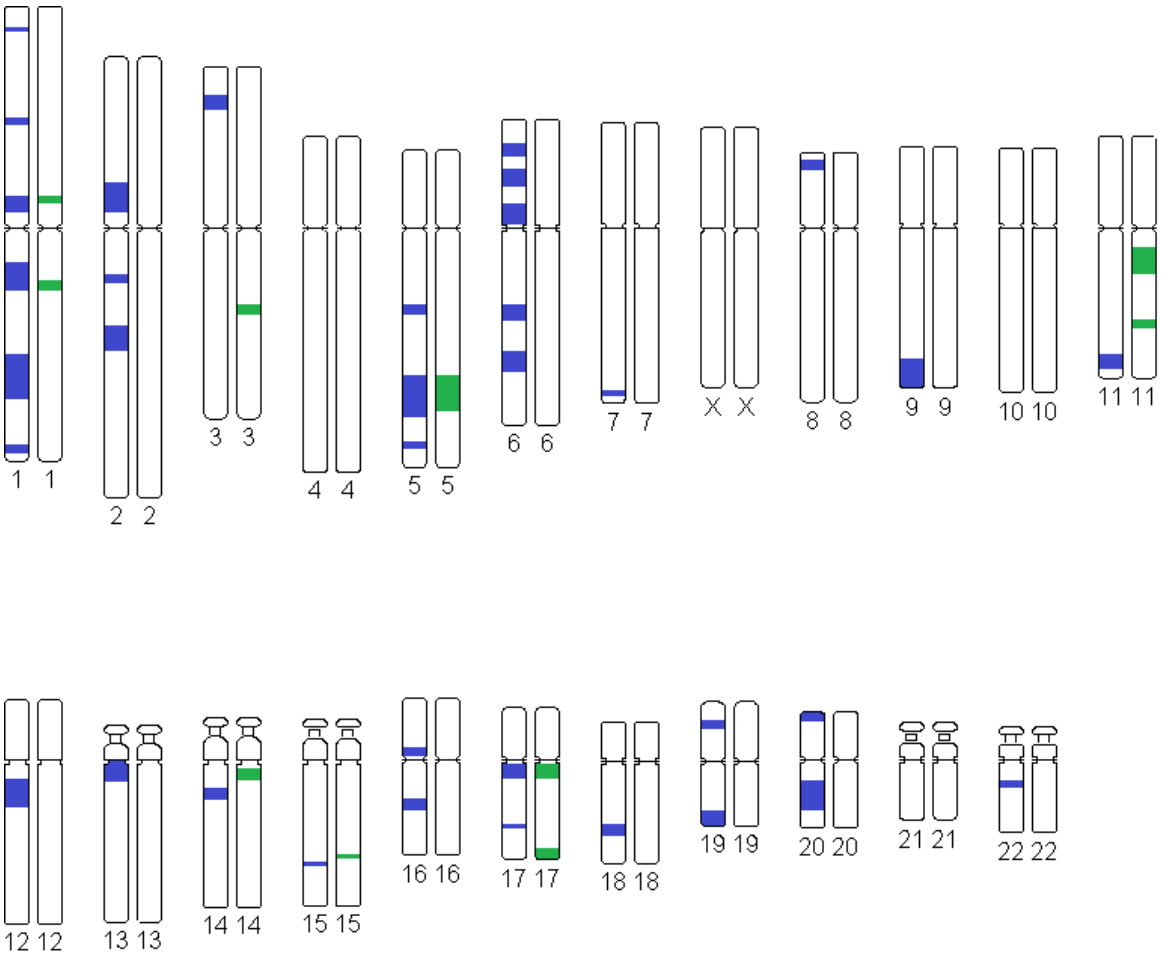


Figure 5.3.: Karyogram showing locations of genes with strict replications (in the same genetic variant) in high-quality studies for both diseases; left chromatid, psoriasis; right chromatid, atopic eczema.

To provide a more strict representation of the genetic predispositions to atopic eczema and psoriasis, only genetic variants which have been replicated (strict replication) in studies which meet certain quality criteria like for example a sufficient sample size of at least 100 participants were summarized in Figure 5.3.

Yet both figures show an overlap of chromosomal locations with significantly associated genes and most of these locations contain more than one candidate gene for each disease. As a consequence, all of these candidate genes for atopic eczema and psoriasis mapping to a shared chromosomal location were listed in Table 5.1.

5.2.1. Divergent candidate genes in shared chromosomal locations

In about 40% of the shared chromosomal locations candidate genes did not match (Table 5.1). On chromosome 2q12, for example, IL1F7 was associated with psoriasis while IL1RL1 was found to be related to atopic eczema. Yet both genes encode a member

of the interleukin 1 cytokine family, indicating a similar pathway in the pathogenesis of both diseases. Replications are still missing for both of them.

On chromosome 3p25, there are divergent candidate genes which are involved in the immune response. PPARG was associated with Canadian psoriasis patients and IL5RA showed significant association in a Korean atopic eczema sample. While the former encodes the regulatory protein PPAR-γ, the latter determines the expression of the alpha subunit of the interleukin 5 receptor. Here, too, replication of the associations is still expected.

In location 3p21.3, there were positive reports for candidate genes encoding chemokine receptors and toll-like receptors, respectively. CX3CR1 was associated with psoriasis while CCR2 was associated with psoriatic arthritis but not with skin-type psoriasis. For atopic eczema, the TLR9 variant -1237C/T showed over-transmission in a family sample. The corresponding gene encodes a member of the toll-like receptor family which is involved in the activation of innate immunity. Two replication samples did not support this finding, however.

On chromosome 6q23.3, a TNFAIP3 variant showed significant association with psoriasis in two genome-wide association studies. The gene is involved in the immune response by regulating NF-κB signaling and acting downstream of TNF-α. For atopic eczema, a gene important for the function of cytokine signaling was reported. It encodes the alpha chain of the gamma interferon receptor (IFNGR1), but was not replicated so far.

In location 12q13, more than one genetic association has been found for psoriasis. While the association of IL23A was detected and replicated in three genome-wide association analyses, a marker SNP in RPS26 showed a significant signal in only one of these genome-wide association analyses. Polymorphic VDR sites have been widely investigated as well. Two of them showed replicated association, but performed meta-analyses did no reach statistical significance.

For atopic eczema, there was a negative report on VDR polymorphisms and only a single association with the TIMELESS gene. While a deletion polymorphism was more frequent in Korean patients, a different insertion polymorphism was over-transmitted in Australian families, but not in Asian families.

On chromosome 13q14.2, two distinct genes were significantly associated with the respective diseases as well. HTR2A encoding a serine peptidase showed evidence of association with late-onset psoriasis in a Thai population while two variants of the asthma susceptibility gene PHF11 were over-transmitted in Australian atopic eczema families.

The location 17q11.2-q12 contains a number of different chemokine ligands. While CCL2/MCP1 was related to psoriasis patients, CCL3/MIP1A and CCL5/RANTES were found to be associated with atopic eczema. In detail, four polymorphisms in CCL3 showed significant results in a small Japanese case-control study and the CCL5 variant -401G/A was replicated in three independent populations. Apart from the chemokine ligands, a SNP in the polymorphic NOS2 gene reached genome-wide significance for association with psoriasis in a genome-wide scan.

Table 5.1.: Shared chromosomal locations for atopic eczema and psoriasis

		Gene(s)$^{+}$	
Chr	**Location**	**Psoriasis**	**Atopic eczema**
1	1p13.3	GSTM1, PTPN22**	GSTM1**
	1q21.3	FLG*, LCE-cluster**, IVL, SPRR-family, PGLYRP3/4, LELP1, PRR9, SMCP	FLG**, HRNR**
	1q31-q32	IL10**, IL19**, IL20*	IL10
2	2q12	IL1F1	IL1RL1
3	3p25	PPARG	IL5RA
	3p21.3	CCR2, CX3CR1	TLR9
	3q21	CSTA, SLC12A8*	CSTA
4	4q26-q27	IL2, IL2-IL21	IL2*
5	5q31.1-q33.1	IL12B**, IL13**, IL4, ADRB2, TNIP1**, SLC22A4/5, ANXA6, IRGM	IL12B, IL13**, IL4, ADRB2, SPINK5**, CD14**, IL5*, CSF2*, RAD50
6	6p21.3	TAP1, TAP2, HLA-Genes**, MICA**, CCHCR1**, CDSN**, TNF**, MICA/HLA-B, MICB, PSORS1C1*, PSORS1C2*, PSORS1C3*, CDKAL1**, LTA**, POU5F1**, CBF**, c6orf10**, RXRB, HCP5, C2, C4A/B	TAP1
	6p12	VEGFA**	VEGFA
	6q23.3	TNFAIP3**	IFNGR1
8	8p23.1	DEFB**	DEFB1*
11	11q22.2-q22.3	IL18	IL18**
12	12q13	IL23A**, RPS26**, VDR**	TIMELESS*
	12q14	IFNG	IFNG
13	13q14.2	HTR2A	PHF11
16	16p12.1-p11.2	IL4R	IL4R*
	16q21	NOD2**	NOD2*
17	17q11.2-q12	CCL2, NOS2**	CCL3, CCL5**
	17q25.3	RAPTOR, GRIN2C, FDXR	SOCS3**
19	19p13.3	KIR2DL5A	TBXA2R
	19q13.4	KIR2DS1**/2/3, KIR2DL2	KLK7, NLRP12
20	20p13	ADAM33**, SIGLEC1	ADAM33
22	22q11.23	GSTT1, MIF**	GSTT1

Chr, chromosome; Locus, as published by the *NCBI*; Gene(s), given by their 'Official Gene Symbol' (aliases, gene name and location provided in the List of Genes). $^{+}$, corresponding positive reports and references are provided in Table A.1 on page 225 for atopic eczema and in Table B.1 on page 235 for psoriasis; *, loose replication in deviating genetic variants; **, strict replication in the same genetic variant.

On chromosome 17q25.3, the susceptibility loci ATOD4 and PSORS2 overlap. Here, SOCS3 encoding a suppressor of cytokine signaling showed replicated association with atopic eczema. In contrast, candidate genes for psoriasis including RAPTOR, FDXR and GRIN2C were only associated in single studies.

In location 19p13.3, a killer Ig-like receptor gene, KIR2DL5A, showed significant association to Japanese psoriasis patients. It plays a role in the immune response as said killer Ig-like receptors are bound to natural killer cells. Meanwhile, TBXA2R encoding a thromboxane receptor, was associated with a subgroup of extrinsic atopic eczema in a Japanese cohort. However, both of these putative associations lack replication.

On chromosome 19q13.4, further killer Ig-like receptor genes including KIR2DL2, KIR2DS1, KIR1DS2 and KIR2DS3 showed evidence of association in a Canadian psoriatic arthritis cohort. Still, the only replicated gene is KIR2DS1 which had already shown higher frequencies in two former psoriasis samples.

For atopic eczema, insertions in KLK7 and NLRP12 were more frequent in patients than in controls. Replication was attempted for the AACCins polymorphism of KLK7 but failed. KLK7 encodes kallikrein-related peptidase 7 while NLRP12 encodes a protein that suppresses inflammatory responses in activated monocytes.

For more information on the positive reports in divergent candidate genes in shared chromosomal locations and the corresponding references see Table A.1 on page 225 as well as chapter 3 for atopic eczema and Table B.1 on page 235 as well as chapter 4 for psoriasis.

5.2.2. Shared candidate genes

Concerning the remaining 60% of overlapping chromosomal locations, significant associations with shared candidate genes can be found. An overview on all the shared candidate genes and their respective risk variants is provided in Table 5.2.

The locations 1p13.3 and 22q11.23 contain genes encoding distinct classes of glutation S-transferases. Null mutations of GSTM1 and GSTT1 were tested for associations in both diseases. For psoriasis, only one German case-control study reached statistical significance for the said null alleles while another study failed to detect an association. In the case of atopic dermatitis, four studies investigated GSTM1 and GSTT1. A significant association with the GSTM1 null mutation was confirmed in three of these studies while GSTT1 was only associated once. Another candidate gene named PTPN22 on chromosome 1q13.3 was replicated for psoriasis, not yielding significance in a performed meta-analysis. It was not investigated in atopic eczema though.

Chromosome 1q21.3, where susceptibility loci ATOD2 and PSORS4 coincide, is the location of the epidermal differentiation complex (EDC). It contains a number of genes which could cause an epidermal dysfunction as witnessed in atopic eczema and psoriasis. Consequently, replicated associations with candidate genes in this region were established for both diseases.

For FLG there is strong evidence of association with atopic eczema, large meta-analyses established common null mutations R501X and 2282del4 as the major risk factors in European populations. These two FLG mutations were not associated with

psoriasis in three independent studies. Yet two other single nucleotide polymorphisms, rs11584340 and rs1858483, showed a positive report in one association study each (loose replication).

Besides FLG, other genes in the epidermal differentiation complex showed significant associations. For psoriasis, there were positive reports on a functional variant near IVL, several PGLYRP4 variants and especially the LCE3C/B deletion polymorphism. While the former variants were not replicated, the latter was confirmed in various association studies, a multi-center study and a meta-analysis.

For atopic eczema, there was evidence for additional risk factors in the epidermal differentiation complex as well. In a genome-wide association scan a marker SNP was in linkage disequilibrium with several genes in the EDC especially hornerin (HRNR). Single investigations on the LCE3C_LCE3B deletion, IVL or other genes did not yield significant association estimates for atopic eczema though.

On chromosome 1q31-q32, there are a number of genes encoding different interleukins. Particularly IL10 is of interest as there were associations with both diseases. Variants -1082A/G and -2763A/C were associated with psoriasis while -819T/C showed relation to atopic eczema. Replication was achieved for -1082A/G and psoriasis, but no association was detected in four independent studies on atopic eczema. For psoriasis, there were even more replicated associations with different interleukin genes (Table 5.1).

On 3q21, there had already been linkage peaks for both atopic eczema (ATOD1) and psoriasis (PSORS5). The location contains a common candidate gene for both diseases: CSTA. It is of functional relevance as its gene product plays an important role in epidermal differentiation and maintenance. Some deviating SNPs were associated with atopic eczema on the one hand and psoriasis on the other hand (Table 5.2). Yet none of them was replicated in an independent sample and the psoriasis risk variant 162T/C was not associated with atopic eczema.

An additional candidate gene for psoriasis in this location is SLC12A8, a member of the solute carrier family. There were single positive reports for different SNPs in independent family and case-control studies (loose replication). Yet it was not investigated for atopic eczema.

On chromosome 4q26-q27, the putatively shared candidate gene is IL2. This makes sense as both psoriasis and atopic eczema are complex immunologically mediated disorders in which interleukins play an important role. Indeed, the SNP rs2069762 showed single positive reports for both diseases. For atopic eczema, an additional polymorphism showed evidence of association (loose replication) while a genome-wide scan for psoriasis found significant association signals in the region flanked by IL2 and IL21.

The location on 5q31.1-q33.1 contains susceptibility loci ATOD6 and PSORS11 as well as three shared candidate genes. All of them encode interleukins or parts of interleukins. Especially the IL13 variant rs20541 is a weak but established psoriasis risk factor which was validated in a meta-analysis. Variant rs1800925 was not associated as often, but still replicated. Both polymorphisms showed replicated associations with atopic eczema as well. Thus, IL13 seems to be a shared candidate gene for both psoriasis and atopic eczema.

In the same location, IL12B is another established risk gene for psoriasis susceptibil-

ity. Single nucleotid polymorphisms rs3212227 and rs6887695 have been examined by means of meta-analysis and showed significant outcomes. The SNP rs3212227 was also associated with atopic eczema in a single positive report.

At the same time, a common single nucleotide polymorphism in IL4 showed evidence of association with both diseases. In contrast to IL13, the association with -590C/T was replicated for atopic eczema only. Polymorphisms in ADRB2 encoding the beta-2-adrenergic receptor were not replicated for either disease.

In addition, there are more candidate genes for psoriasis and atopic eczema individually. While a genome-wide association scan for psoriasis mapped to TNIP1, a gene involved in NF-κB signaling, atopic eczema was repeatedly associated with genes like IL5, CD14, CSF2 and SPINK5. A variant in the latter gene was replicated, but no significant result was achieved in a performed meta-analysis.

Another overlap is located within the psoriasis susceptibility locus PSORS1 on chromosome 6p21.3. The shared candidate gene is TAP1 which encodes a transporter protein. Still, a polymorphism in this gene has only been associated once with each disease. Apart from this, the locus contains many candidate genes for psoriasis. There is strong support for HLA-C being the major susceptibility gene in PSORS1 while other candidate genes like CDSN, TNF or MICA show weaker association estimates (Table 5.2). There were no investigations on these psoriasis risk genes for atopic eczema.

On chromosome 6p12, psoriasis and atopic eczema shared another common candidate gene: VEGFA. It encodes the vascular endothelial growth factor which induces T cell migration into inflamed skin on the long run. An existing meta-analysis supports +405G/C as a significant risk variant for psoriasis, besides other less studied variants including -460C/T. In addition, there was support for an association with atopic eczema as well. The VEGFA variant -1154G/A reached significance in a Polish case-control study, but was not replicated so far.

In location 8p23.1, β-defensin genes (DEFB) are putatively associated with both diseases. They encode antimicrobial peptides which contribute to epithelial barrier function which in turn plays an important role in the pathogenesis of chronic inflammatory skin diseases like atopic eczema and psoriasis. In addition to that, they are said to have cytokine-like properties playing a role in the innate immune response. While psoriasis was associated with a higher genomic copy number of DEFB genes in two independent case-control samples, atopic eczema showed evidence of association with variants DEFB1 in two different samples (loose replication).

On chromosome 11q22.2-q22.3, there were positive reports for a shared SNP. The IL18 variant -137G/C was associated once with psoriasis and twice with atopic eczema. While further variants were detected for atopic eczema, for psoriasis it remained merely a single positive report.

Similarly, a common variant was discovered on chromosome 12q14 in a gene encoding an immune mediating cytokine. The IFNG polymorphism 874A/T was associated with a small Egyptian atopic eczema cohort and a larger Polish psoriasis cohort. Yet for both diseases there was no replication since then.

More support was achieved for the interleukin 4 receptor gene (IL4R) on chromosome 16p12.1-p11.2. There were positive reports for atopic eczema and psoriasis in two

Table 5.2.: Shared candidate genes for atopic eczema and psoriasis

			Variant		Associations^{+}	
Chr	**Location**	**Gene**	**PS**	**AE**	**PS**	**AE**
1	1p13.3	GSTM1	null allele		1	3
	1p21.3	FLG	rs1858483	R501X	1	19
			rs11584340	2282del4*	1	18
	1q31-q32	IL10	- 1082A/G	- 819T/C	2	1
			-2763A/C	-	1	-
3	3q21	CSTA	162T/C	344C/T	1	1
4	4q26-q27	IL2	rs2069762		1	1
			-	rs2069763	-	1
5	5q31-q32	IL13	rs20541		8	3
			rs1800925		3	2
		IL12B	rs3212227		15	1
		IL4	- 590C/T		1	2
			rs6887695*	-	12	-
		ADRB2	Arg16Gly	Gln27Glu	1	1
6	6p21.3	TAP1	637		1	2
			-	333	-	1
	6p12	VEGFA	+ 405G/C	- 1154G/A	2	1
			- 460C/T*	-	2	-
8	8p23.2-p23.1	DEFB	CNV	- 2266T/C	2	1
			-	668C/G*	-	1
11	11q22.2-22.3	IL18	- 137G/C		1	2
			-	rs795437*	-	1
12	12q14	IFNG	874A/T		1	1
16	16p12.1-p11.2	IL4R	- 326A/C		1	1
			- 186G/A		1	1
			-	Q551R*	-	3
	16q21	NOD2	R702W		2	1
			rs2076752	2722G/C	1	1
20	20p13	ADAM33	rs597980	rs2853209	3	1
			rs512625	-	2	-
22	22q11.23	GSTT1	null allele		1	1

Chr, chromosome; Locus, as published by the *NCBI*; Gene, given by its 'Official Gene Symbol' (aliases, gene name and location provided in the List of Genes); Variant, given by its base number (*GenBank*) or SNP ID (*NCBI SNP database*); Associations, given by number of positive reports (corresponding references see Tables B.1, p. 235 and A.1, p. 225); Underlined genes showed replicated associations with both diseases, though not in the same variant. *, further variants showed association as well; $^{+}$, corresponding positive reports and references are provided in Table A.1 on page 225 for atopic eczema and in Table B.1 on page 235 for psoriasis.

variants, -326A/C and -186G/A. These were not replicated, but a third variant showed association with atopic eczema. For psoriasis, on the contrary, there was no additional evidence.

On chromosome 16q21, there is another promising candidate gene with a shared risk variant. NOD2 has functional relevance as its gene product is involved in NF-κB signaling and in the immune response in general. The polymorphism R702W was associated twice with psoriasis and once with atopic eczema. A further variant each, showed additional significant association estimates. Thus, NOD2 was replicated for both psoriasis and atopic eczema.

The overlapping location on chromosome 20p13 contains a susceptibility locus for atopic eczema (ATOD3) and a linkage region for psoriasis as well as a putative risk gene

for both diseases: ADAM33. Yet there was only replicated evidence of psoriases while there was merely one positive report for atopic eczema (Table 5.2).

In summary, most shared candidate genes lacked replication. Either there was strong support for one disease and only weak for the other or weak support for both diseases. Yet some genes showed replicated association with both diseases: FLG, IL13, NOD2 and the DEFB cluster (underlined in Table 5.2). In the latter, psoriasis showed association with a higher genomic copy number of DEFB genes in two independent samples while atopic eczema showed loose replication for DEFB1.

FLG showed association for common null mutations in atopic eczema validated by meta-analyses and loose replication for different SNPs in psoriasis. Similarly, NOD2 showed strict replication for R702W in psoriasis and loose replication for R702W and another SNP in atopic eczema. Only IL13 reached a higher degree of evidence for both diseases with three strict replications for atopic eczema and a positive meta-analysis for psoriasis in an identical variant.

For more information on the positive reports in shared candidate genes and the corresponding references see Table A.1 on page 225 as well as chapter 3 for atopic eczema and Table B.1 on page 235 as well as chapter 4 for psoriasis.

5.3. Shared negative reports on genetic predispositions

There were a number of common genes which seemed to be candidates for both chronic inflammatory skin diseases due to their functional relevance. For example, genes involved in epidermal differentiation or in the immune response. Yet some of these putative candidate genes turned out to be much less favorable than initially predicted as they did not show significant associations with either disease. All negative reports with corresponding references are listed in A.2 on page 230 for atopic eczema and in B.2 on page 243 for psoriasis.

Genes involved in epidermal differentiation. As an impaired epidermal differentiation contributes to the development of psoriasis and atopic eczema, genes in the epidermal differentiation complex on chromosome 1q21 were thought to be suitable candidates. While FLG, IVL or LCE genes demonstrated evidence of association, however, a number of others did not.

For example, loricrin (LOR) which contributes to the cornified cell envelope in epidermal cells showed negative reports for both atopic eczema and psoriasis. Similarly, members of the S100 family as well as SPRR1A and SPRR1B did not show proof of association. (Tables A.2, p. 230 and B.2, p. 243)

Genes involved in the immune response. As a dysregulated immune response is observed in the pathogenesis of chronic inflammatory skin diseases like atopic eczema or psoriasis, involved genes seem reliable candidates for their susceptibility. For example, IL12RB2 on chromosome 1p31.3-p31.2 encoding part of the interleukin 12 receptor which

has influence on the Th1/Th2 balance. Yet no association between genetic variants and either disease could be identified.

Similarly, IL12A encoding the α subunit of interleukin-12 did not show evidence of association unlike the gene encoding the β subunit (IL12B). The latter has been established as a risk factor for psoriasis susceptibility by meta-analysis and for atopic eczema there was a single positive report as well.

Further mediators of inflammation including interleukins have been investigated in both diseases. Interestingly, neither IL8 nor IL17F showed positive reports. Especially IL17F was a strong candidate as it is produced by Th17 cells which are expressed in the inflamed skin of psoriasis patients and less but measurable of atopic eczema patients.

C-C chemokines are further candidate genes for the susceptibility to chronic inflammatory skin diseases. They are believed to play an important role in the pathogenesis by attracting and activating immune cells. Yet the chemokine receptor CCR5 was not associated with either psoriasis or atopic eczema.

In addition to that, candidate gene ICAM1 encoding intercellular adhesion molecule 1 resulted unlikely as well. The protein is involved in the immune response by its contribution to T cell activation, but there was no association with the diseases in question. (Tables A.2, p. 230 and B.2, p. 243)

5.4. Contrasting reports on genetic predispositions

There were many reports on differing genetic predispositions to psoriasis and atopic eczema of course. This can be witnessed in tables A.1 on page 225 and B.1 on page 235. For certain candidate genes, however, positive reports for the one disease clash with negative reports for the other, promoting them as independent risk factors. If a risk factor for the one disease has not been tested in the other, it remains unclear.

This is the case for major psoriasis risk factors on chromosome 6p21.3. Neither HLA-C nor CDSN or MICA have been tested for atopic eczema, but there were a number of negative reports for TNF. The two variants -308G/A and -238G/A did not show proof of association in a number of independent studies on populations from European and Asian background (Table A.2, p. 230).

For genes in the epidermal differentiation complex (EDC) on chromosome 1q21, many investigations in the respective other disease were carried out. For example, the LCE3C/B deletion was validated in various association studies, a multi-center study and a meta-analysis for psoriasis while there was a negative report for atopic eczema.

For the two common FLG null mutations R501X and 2282del4 it was the other way round. They are established risk factors for atopic eczema in European populations, but were not associated with psoriasis in three independent studies. Yet there were positive reports for variants rs11584340 and rs1858483 (loose replication).

Two further risk genes were not investigated in the respective other disease: IL23R and CMA1. Thus, no statement whether these are independent risk genes can be given. Yet for CMA1 there is a hypothesis that mast-cell chymase does not promote inflammation in psoriasis [169] and there were no elevated levels either [21].

6. Conclusions

The research on the genetic backgrounds of atopic eczema and psoriasis passed through different stages using a number of different approaches. While twin studies promoted both heritable and environmental factors for the development of the diseases, genetic linkage analyses led to the discovery of susceptibility loci in the genome. Candidate gene studies tested several genes for association with the respective disease, genome-wide association analyses scanned the genome for association signals and meta-analyses were carried out to validate results on promising candidate genes.

These investigations accumulated a large amount of data on the genetics of atopic eczema and psoriasis. In a first step, this data was identified, sorted and tabulated in large surveys in order to provide a comprehensive overview. Next, additional meta-analyses were performed on well-studied genetic variants to further validate the research results on both complex diseases. Finally, a comparison of genetic predispositions tried to answer the question whether there is a shared genetic background of the two chronic inflammatory skin diseases.

The conclusions to be drawn from the prepared surveys and meta-analyses on the genetic predispositions to atopic eczema and psoriasis as well as their comparison shall be discussed in the following. The aim was to evaluate the current insights into the genetics of the two chronic inflammatory skin diseases and the question of a shared genetic background.

6.1. Insights into the genetics of atopic eczema

As mentioned, first evidence of genetic factors underlying the development of atopic eczema was provided by twin studies. They reported higher concordance rates for monozygotic than for dizygotic twins. Next, genetic linkage analyses proposed nine susceptibility loci for atopic eczema (Figure 3.1), but only few of them were consistently replicated. For example, ATOD1 on chromosome 3q21 and ATOD9 on chromosome 3p24 were established by more than one investigation. ATOD2 on chromosome 1q21 was not confirmed by further linkage studies, but by the results of candidate gene studies and genome-wide association studies.

The said locus on 1q21 contains the epidermal differentiation complex (EDC) involving genes relevant for epidermal barrier function and by this putatively relevant for the pathogenesis of atopic eczema. From a large number of genes, FLG has been supported as the major risk gene in the EDC and for atopic eczema in general. The two common FLG null mutations R501X and 2282del4 showed significant associations in European populations validated by two existing meta-analyses and additional association studies.

Asian and other populations, in contrast, seem to depend on different FLG mutations.

A genome-wide association study found highly significant association signals in the epidermal differentiation complex on chromosome 1q21 as well. The marker SNP rs6661961 mapping 156kb from FLG was in high linkage disequilibrium and lost significance when excluding FLG null mutation carriers. In contrast, the single nucleotide polymorphism rs877776 near HRNR remained significant after stratification. This accounts for additional genetic risk factors in the EDC besides the major risk gene FLG.

In addition, the genome-wide association scan indicated another risk locus on chromosome 11q13.5. The marker SNP rs7927894 was repeatedly associated with atopic eczema in five sample sets form European origin. It was in strong linkage disequilibrium with C11orf30 and had been associated with Crohn's disease as well, suggesting functional relevance for inflammation or autoimmunity in general. Asian populations did not seem to be associated with this genetic factor, as replication in a Japanese cohort failed.

Further evidence for association with atopic skin inflammation was given for CMA1 on chromsome 14q11.2. Investigations included ten candidate gene studies, six of which were validated in an additional meta-analysis. The result showed only a weak effect, conferring a 1.37 fold risk to atopic eczema. Consequently, its contribution to the development of the disease is rather low compared to a 3.58 fold risk conferred by the common FLG variants. The newly performed meta-analysis of another well-studied candidate gene derived from a related skin disease, SPINK5, did not reach statistical significance (Figure 3.10).

Apart from this, there have been positive reports for 55 other candidate genes with twelve showing loose replications in deviating genetic variants and another twelve showing strict replications in the same genetic variant. Yet none of them reached a high level of significance. Interestingly, unlike FLG most of the replicated genes encode immune mediators or other pro-inflammatory factors like for example interleukin-13 and interleukin-18 or chemokines like CCL5 (Figure 3.9).

6.2. Insights into the genetics of psoriasis

Similar to atopic eczema, first evidence of heritable factors underlying the development of the disease was provided by twin studies. They consistently reported higher concordance rates for monozygotic than for dizygotic twin pairs. Next, genetic linkage analyses proposed twelve susceptibility loci for psoriasis and one for psoriatic arthritis (Figure 4.1). Most of them have been replicated and especially for PSORS1 on chromosome 6p21.3 there was strong evidence.

The said locus contains major histocompatibility complex (MHC) genes which are important for antigen presentation and by this putatively important for the pathogenesis of psoriasis. From a large number of genes, HLA-C has been supported as the major risk gene in PSORS1 and for psoriasis in general. The HLA-Cw*0602 allele was investigated in 53 independent studies, 44 of which were validated in an additional meta-analysis. The result showed a strong effect, conferring a 4.73 fold risk to psoriasis in both European and Asian populations. Especially subgroups of early-onset psoriasis vulgaris and guttate

psoriasis showed pronounced associations.

Apart from HLA-C, the PSORS1 locus contains 17 other candidate genes with positive results, six of them being significantly validated by additional meta-analyses. While the MICA triplet repeat $(GCT)_9$ was mainly associated with psoriatic arthritis, CDSN polymorphism +1243C and haplotypes showed an onset-dependent association with early-onset psoriasis vulgaris in European populations. Similarly, TNF variant -308A demonstrated a pronounced association with early-onset psoriasis vulgaris patients while variants -238A and -857T were especially associated with psoriatic arthritis patients from Europe.

For SNP n.9 the highest estimates were achieved for cases with guttate psoriasis. Both CCHCR1*WWCC and HLA-B57 showed strong effects independent from clinical variant, onset type and ethnicity. Still, HLA-C remains the major psoriasis risk gene demonstrating the highest association estimate of all meta-analyses (Figure 4.82). Equally high association estimates for markers near HLA-C in all genome-wide association scans provided additional evidence for this hypothesis.

As only about one tenth of the individuals with variations in PSORS1 develop psoriasis, additional genetic risk factors were suspected. And indeed, the first genome-wide association scan revealed IL12B and IL23R as additional susceptibility determinants mapping to previously established risk loci on chromosome 1q31.3 (PSORS7) and on chromosome 5q31.1-q33.1 (PSORS11). Both have been validated by new meta-analyses showing significant results.

For PSORS11 there were further reports: A performed meta-analysis of the IL13 polymorphism rs20541 demonstrated association with psoriasis and particularly psoriatic arthritis in populations from European descent while genome-wide association scans found replicated evidence for TNIP1. Relating to susceptibility loci, significant signals in genome-wide association scans validated two further loci on chromosome 19p13 (PSORS6) and on chromosome 20q13 (PSORS12).

The psoriasis risk locus PSORS4 on chromosome 1q21 contains the epidermal differentiation complex (EDC) involving genes relevant for epidermal barrier function and putatively relevant for the pathogenesis of psoriasis. Here, especially a deletion of LCE3C/B has shown significant associations in a multi-center study, an existing meta-analysis and additional studies.

In addition, there was further evidence for several candidate genes lying outside established susceptibility loci. For example, VEGFA on 6p12 encoding the vascular endothelial growth factor was associated with an increased risk for psoriasis in a number of studies, validated at least for Asian populations by an existing meta-analysis.

Similarly, ACE on 17q23.3 encoding angiotensin converting enzyme was thought to play a role in the pathogenesis of psoriasis. As a consequence, an insertion polymorphism was tested for association in a number of candidate gene studies and was validated in a newly performed meta-analysis showing a weak effect.

Apart from this, there have been positive reports for over 100 other candidate genes with ten showing loose replications in deviating genetic variants and another 40 showing strict replications in the same genetic variant. While meta-analyses on VDR, PTPN22, IL10 and IL1RN did not yield significant results, genome-wide association studies added

associations with 27 single nucleotide polymorphisms.

For example, ERAP1 on chromosome 5q15 as well as genes involved in NF-κB signaling like TNIP1 on chromosome 5q32-q33.1, TNFAIP3 on chromosome 6q23, TRAF3IP2 on chromosome 6q21 and NFKBIA on chromosome 14q13 and genes involved in IFN-signaling like IFIH1 on chromosome 2q24 were even replicated in independent genome-wide scans (Figure 4.81).

6.3. Is there a shared genetic background?

Both atopic eczema and psoriasis are complex diseases with a multifactorial genesis. As a consequence, environmental triggers contribute to their development together with multiple genes. The presence of some common features as well as parallels in the pathogenesis make a shared genetic background conceivable.

In addition, genetic linkage analyses showed overlaps of susceptibility loci in six chromosomal locations mapping to 1q21, 5q31.1-q33.1, 3q21, 20p, 17q25, and the q arm of chromosome 4 (Figure 5.1). As chromosome 1q21 contains the epidermal differentiation complex (EDC) involving genes relevant for epidermal barrier function and by this putatively relevant for the pathogenesis of both diseases, candidate genes were suspected here. And indeed, there were a number of positive reports.

For atopic eczema, FLG was established as the major risk gene in the EDC and the disease in general, while a deletion in the LCE cluster showed strong evidence of association with psoriasis. Yet both the FLG null mutations R501X/2282del4 and the LCE3C_LCE3B deletion polymorphism were not related to the respective other disease.

Interestingly, two other single nucleotide polymorphisms in the FLG gene showed a loose replication for psoriasis. At the same time, a genome-wide scan for atopic eczema indicated the presence of additional risk factors in the EDC. But as the LCE3C_LCE3B deletion polymorphism was associated with psoriasis but not atopic eczema, deviating genetic factors underlying the epidermal barrier dysfunction in the pathogenesis of the two chronic skin diseases seem more likely (Table 5.1).

The shared susceptibility locus on chromosome 5q31.1-q33.1 showed less within-locus heterogeneity. As it contains interleukin genes which are important for the immune response and by this putatively relevant for the pathogenesis of chronic inflammatory skin diseases like atopic eczema and psoriasis, further candidate genes were assumed in this location. Here, too, a number of associations were reported.

For psoriasis, IL12B is an established risk gene and one of the risk variants showed a positive report for atopic eczema as well. But as a replication study is missing, no clear assessment can be made on this coincidence. For a common single nucleotide polymorphism in IL4, there were additional positive reports for both diseases. In this case, however, there was significant replication for atopic eczema only.

Remarkably, there were replicated positive reports for two shared variants in IL13. While the association of rs20541 with psoriasis was validated by a comprehensive meta-analysis, there were at least three independent replications for atopic eczema. In addition to that, the SNP rs1800925 showed repeated positive reports for both diseases as well.

Consequently, IL13 seems to be a shared candidate gene.

For the remaining overlaps of susceptibility loci on chromosomes 3q21, 20p, 17q25 and 4q the results of candidate gene studies and genome-wide association scans were not as convincing. In the majority of cases, shared genetic associations were discovered but not replicated.

For example, the locus on chromosome 3q21 contains CSTA which encodes a protein involved in epidermal differentiation and maintenance like filaggrin or late cornified envelope proteins. For both atopic eczema and psoriasis there were single positive reports for distinct CSTA risk variants. Yet an investigation of the putative psoriasis risk variant in atopic eczema did not reach significance.

For the overlapping linkage region on chromosome 20p there was a common candidate gene as well. Distinct polymorphisms in ADAM33 were found to be correlated with an increased incidence of atopic eczema or psoriasis, respectively. Yet there was only replicated evidence for psoriases.

On chromosome 17q25 there was high within-locus heterogeneity. No significant associations with a shared candidate gene were reported. While SOCS3 encoding a suppressor of cytokine signaling demonstrated replicated association with atopic eczema, genetic variants in RAPTOR, FDXR and GRIN2C showed only single positive reports for an association with psoriasis.

An overlap on the q arm of chromosome 4, more precisely 4q22.1, did not reveal any candidate genes for atopic eczema. Yet telomeric on 4q26-q27, a common single nucleotide polymorphism in IL2 was associated with both diseases. For atopic eczema an additional SNP showed evidence of association, while a genome-wide scan for psoriasis found significant signals in the region flanked by IL2 and IL21. However, these findings have not been replicated to date.

Even if there was no overlap of susceptibility loci on chromosome 16q21, there were still positive reports for a shared genetic risk variant in NOD2. The corresponding gene product has functional relevance for the immune response as it is involved in NF-κB signaling. Polymorphism R702W was associated twice with psoriasis and once with atopic eczema. In addition, there were single positive reports for a further variant each, implying NOD2 as a shared candidate gene.

Similarly, polymorphisms in the DEFB gene cluster on chromosome 8p23.1 were associated with both diseases. While a higher genomic copy number of DEFB genes was related to psoriasis in two independent samples, the was loose replication for deviating variants in the DEFB1 gene and atopic eczema.

In summary, at least two overlapping chromosomal locations were of special interest. First, the epidermal differentiation complex (EDC) on 1q21 which contains FLG null mutations predisposing to atopic eczema and a deletion in the LCE cluster associated with psoriasis. FLG even showed loose replications with psoriasis in deviating variants. Second, chromosome 5q31.1-q33.1 where IL13 shows replicated associations with both diseases. For the remaining susceptibility loci, most shared candidate genes lacked replication or there was a high within-locus heterogeneity. Merely in the DEFB gene cluster and NOD2 there was an additional overlap of candidate genes. Yet numbers of replications were low and partly in deviating variants (Table 5.2).

7. Summary

Atopic eczema and psoriasis are two of the commonest chronic inflammatory skin diseases with similarly high prevalences, especially in Northern European countries. Shared features of chronic lesions are a dry, scaly skin and a thickened epidermis accompanied by an inflammatory infiltrate. The disease mechanisms leading to these clinical and histological pictures involve a dysfunction of epidermal cells and a dysregulation of T cells. Both are complex traits with a multifactorial genesis in which environmental triggers interact with several susceptibility genes. Over the past decades, growing insight into the genetics of atopic eczema and psoriasis was gained and an overlap of susceptibility loci prompted the question of a shared genetic background.

In order to give a comprehensive overview on current research, positive and negative reports on genetic predispositions were searched in *MEDLINE* and were subsequently compiled in large surveys. To be included in the survey, the reports had to comply with certain criteria. If there were sufficient replications for a genetic variant, meta-analyses involving the results of case-control studies were performed. These studies had to meet higher requirements involving a sufficient sample size and the availability of genotyping data or association estimates. Further down the line, gained insights into the genetics of psoriasis and atopic eczema were compared to each other.

For atopic eczema, over 60 genetic predispositions with at least one positive report were ascertained, while 90 candidate genes showed negative reports only. There were strict replications in high-quality studies for a total of 15 polymorphic genes. FLG had been validated by two existing large meta-analyses showing high association estimates and several genome-wide scans. Additional meta-analyses yielded a low association estimate for CMA1 and an insignificant result for SPINK5. Genome-wide scans discovered C11orf30 on chromosome 11q13.5 as a further candidate gene and implicated the existence of an additional risk factor in the EDC near HRNR.

For psoriasis, over 100 genetic predispositions with at least one positive report were identified, while there were exclusively negative reports for 80 candidate genes. A total of 55 polymorphic sites were replicated in independent high-quality studies (strict replication). More than half of the replicated associations were determined in multi-stage genome-wide scans. The LCE3C_LCE3B deletion polymorphism as well as variants in IL12B and IL23R were validated by both genome-wide scans and meta-analyses. Further meta-analyses yielded significant association estimates for ACE, IL13 and genes in the susceptibility locus PSORS1 involving MICA, CDSN, TNF, SNP n.9, CCHCR1, HLA-B and HLA-C. The highest association estimate was achieved for the risk allele HLA-Cw*0602.

A review of susceptibility loci for atopic eczema and psoriasis indicated six overlapping linkage regions. Comparing positive results of association studies, 25 chromosomal

locations containing candidate genes with significant associations for both diseases were determined. In more than half of the cases, variants of a common gene were significantly associated with atopic eczema and psoriasis, but replications mostly failed. Only FLG, IL13, NOD2 and the DEFB gene cluster showed repeated associations with both diseases, though in deviating variants and with a low number of replications. The highest degree of evidence was achieved for IL13 with three strict replications for atopic eczema and a meta-analysis for psoriasis.

The huge numbers of positive reports for genetic predispositions to atopic eczema and psoriasis support a multigenic mode of inheritance for both diseases. Yet many of the putative susceptibility variants have not been replicated and thus may be false positive reports. Still, powerful genome-wide association scans added new genetic risk factors and comprehensive meta-analyses aimed to validate known candidate genes. The major risk genes showing the highest association estimates remain FLG for atopic eczema and HLA-C for psoriasis. Moreover, there was evidence for additional susceptibility factors in the EDC and on chromosome 11q13.5 (C11orf30) for atopic eczema. For psoriasis, variants in IL12B, IL23R, IL13 and VEGFA as well as an ACE insertion and a LCE3C/B deletion in the EDC were supported by meta-analyses. In addition, various other genetic factors were indicated by genome-wide association scans involving ERAP1, TNIP1, TNFAIP3, TRAF3IP2, NFKBIA, SPATA2-RNF114 and IFIH1.

Comparing the genetic predispositions, two overlapping chromosomal locations seemed to be of special interest. First, the epidermal differentiation complex (EDC) on 1q21 which contains FLG null mutations predisposing to atopic eczema and a LCE3C/B deletion associated with psoriasis. FLG even showed significant associations with psoriasis in deviating variants (loose replication). Second, chromosome 5q31.1-q33.1 where IL13 shows replicated associations with both atopic eczema and psoriasis. For the remaining susceptibility loci, most shared candidate genes lacked replication or there was within-locus heterogeneity. Merely in the DEFB gene cluster and in NOD2 an additional overlap of candidate genes was observed. Yet associations were found in different variants and numbers of replications were low.

A. Association studies on genetic predispositions to atopic eczema

A.1. Positive reports for atopic eczema

Table A.1.: Genetic variants providing evidence of association with atopic eczema in at least one published study

Chr	Locus	Gene	Variant	Ass	Size	Diff	Country	Ref
1	1p13.3	GSTM1	null allele	Yes	145	c-a	Korea	[92]
				Yes	34	c	Taiwan	[509]
				No	124	c	Korea	[97]
				Yes	126	c	Russia	[502]
	1q21.3	**FLG***	**R501X, 2282del4**	**META-ANALYSIS**			**Rodriguez 2009 [400]**	
				META-ANALYSIS			**Baurecht 2007 [31]**	
			R2447X	Yes	188	c	Ireland	[420]
				Yes	186	a	UK	[52]
				No	174	c	China	[91]
			S3247X	Yes	188	c	Ireland	[420]
				No	186	a	UK	[52]
			3702delG, 3673delC	Yes	188	c	Ireland	[420]
				No	186	a	UK	[52]
			P478S	Yes	116	c	Taiwan	[510]
			S2554X	No	160	c-a	China	[294]
				No	116	c	Taiwan	[510]
				No	174	c	China	[91]
				Yes	376	c-a	Japan	[126]
				No	105_f	c	Japan	[126]
				Yes	102	-	Japan	[341]
				Yes	143	-	Japan	[343]
			3321delA	Yes	160	c-a	China	[294]
				No	376	c-a	Japan	[126]
				Yes	>212	c-a, e	Japan	[126]
				No	105_f	c	Japan	[126]
				No	102	-	Japan	[341]
				No	143	-	Japan	[343]
			S2889X	No	160	c-a	China	[294]
				No	116	c	Taiwan	[510]
				No	174	c	China	[91]
				Yes	102	-	Japan	[341]
			S3296X	No	160	c-a	China	[294]
				No	116	c	Taiwan	[510]
				Yes	102	-	Japan	[341]
			rs2065958, rs12730241	No	376	c-a	Japan	[126]
				Yes	105_f	c	Japan	[126]
		HRNR*	rs877776	Yes	270_f	c-a	Germany	**G [129]**
				Yes	$\underline{3576}_3$	c-a	Europe	**G [129]**
	1q23	FCER1A*	rs2511211, rs10489854	Yes	1018	a	Germany	[298]
	1q31-q32	IL10	-819T/C	Yes	267	c	Korea	[444]
				No	94	c-a	China	[79]

2	2q12	IL1RL1*	-26999G/A, -27639A/G	Yes	452	c-a	Japan	[432]
	2q22.1	HNMT	314C/T	Yes	122	c	US	[238]
	2q33	CTLA4*	49A/G	Yes	112_f	i	Australia	[222]
				No	66	a	Taiwan	[542]
			CT60A	Yes	112_f	i	Australia	[222]
3	3p26-p24	IL5RA*	rs334809	Yes	646	c-a	Korea	[327]
	3p21.3	TLR9*	-1237C/T	No	136	a	Germany	[350]
				Yes	$\underline{483}_{2f}$	c	Germany	[348]
				No	274	a	Germany	[348]
	3q21	CSTA*	344C/T	Yes	100	a	UK	[494]
	3q22.1	COL6A5*	rs13095825, rs10212372, rs4688761, rs9883988	No	465	c-a	Germany	[167]
			rs13095825, rs16845861, rs10212372, A36603217, rs10934938, rs4688761, A36637742, rs9883988	Yes	$\underline{491}_{2f}$	c	Germany	[442]
	3q25.33-q26	IL12A	IVS2 798A/T	Yes	417	c-a	Korea	[328]
4	4q26-q27	IL2*	rs2069762	Yes	119_f	c-a	Denmark	[95]
				No	73_f	c-a	Denmark	[95]
			rs2069763	No	119_f	c-a	Denmark	[95]
				Yes	73_f	c-a	Denmark	[95]
	4q32	TLR2*	R753Q	No	275	c-a	Germany	[522]
				Yes	78	a	Germany	[1]
				No	129	a	Germany	[350]
	4q34.1-q35.1	IRF2*	-467G/A	Yes	49_f	c	Japan	[336]
5	5p13	IL7R*	rs12516866, rs1053496	Yes	339	c-a	US	[146]
				No	444	c-a	US	[146]
			rs6897932, rs987106	Yes	362	c-a	Germany	[184]
	5q22.1	TSLP*	rs10043985, rs2289276	Yes	399	c-a	US (Africa)	[146]
				No	444	c-a	US (Europe)	[146]
			rs11466749	Yes	444	c-a	US (Europe)	[146]
				No	399	c-a	US (Africa)	[146]
	5q31	IL13*	rs1800925	Yes	82	c	Japan	[311]
				No	894	c	UK	[13]
				No	94	c-a	China	[79]
				No	207_f	c	US	[185]
				Yes	55	c-a	Netherlands	[207]
				No	269_f	i	Canada	[173]
				No	185	a	Japan	[488]
			rs20541	Yes	82	c	Japan	[311]
				No	894	c	UK	[13]
				No	94	c-a	China	[79]
				Yes	185	a	Japan	[488]
				Yes	187	c	Germany	[286]
		RAD50*	rs17772583, rs3798135, rs2240032	Yes	562_f	c-a	Germany	**G [519]**
	5q31.1	CD14*	-159C/T	No	698	c	Netherlands	[440]
				No	82	c	Netherlands	[371]
				Yes	762	c	US	[38]
				Yes	10	c	Germany	[265]
				Yes	154	i	US	[285]
				No	207_f	c	US	[185]
				No	184	c	Germany	[427]
			-1619T/C	No	82	c	Netherlands	[371]
				Yes	698	c	Netherlands	[440]
			rs2569193	Yes	154	i	US	[285]
		CSF2*	-677A/C, -1916T/C	Yes	113	c	UK	[380]
			3606T/C, 3928C/T	Yes	370	i	Canada	[174]
				No	181	c-a	Japan	[412]
		IL4*	-590C/T	No	94	c-a	China	[79]
				No	207_f	c	US	[185]
				Yes	60	c-a, ex	Germany	[346]
				No	14	c-a, int	Germany	[346]
				No	406_f	c	Sweden	[441]
				No	101_f	a	Australia	[121]
				No	190	a	Japan	[468]

				Yes	88	c	Japan	[236]
		IL5*	-703C/T	No	451	a	Japan	[541]
				>Yes	70	a, eos	Japan	[541]
			rs2522411	Yes	646	c-a	Korea	[327]
	5q31.1-q33.1	IL12B*	rs3212227 (1188A/C)	Yes	164	c-a	Japan	[486]
	5q31-q32	ADRB2	Gln27Glu	Yes	12	c-a, int	France	[401]
				No	70	c-a, ex	France	[401]
				No	207_f	c	US	[185]
			rs1042713, rs1800888	No	207_f	c	US	[185]
	5q32	**SPINK5***	**Q420L**	**META-ANALYSIS**				**[Table 3.1, p. 38]**
			Asn368Ser	Yes	124	c-a	Japan	[233]
				No	148	c-a	UK	[508]
				Yes	41_f	c-a	Japan	[337]
				No	200_f	c	Netherlands	[223]
			His396His, IVS12-26C/T, IVS12-10A/G, IVS13-50G/A, IVS14+19G/A	Yes	124	c-a	Japan	[233]
6	6p12	VEGFA	-1154G/A	Yes	100	-	Poland	[550]
	6p21.3	TAP1	333	Yes	20	c	Tunisia	[214]
				No	37	c-a	Japan	[264]
				No	29	c-a	Japan	[263]
			637	Yes	20	c	Tunisia	[214]
				No	37	c-a	Japan	[264]
				Yes	29	c-a	Japan	[263]
	6q23.3	IFNGR1	-56C/T	Yes	78	c-a	Japan	[305]
7	7p15-p14	NOD1*	rs2736726, rs2075817	Yes	454	a	Germany	[521]
				No	189_f	c	Germany	[521]
			rs2975632, rs2075822, rs2907749, rs2907748	No	454	a	Germany	[521]
				Yes	189_f	c	Germany	[521]
X	Xp22	TLR8*	rs2407992	Yes	192_f	c	Denmark	[313]
	Xp22.3	TLR7*	rs179008	Yes	192_f	c	Denmark	[313]
		CRLF2	rs36139698, rs36177645, rs36133495	Yes	444	c-a	US (Europe)	[146]
				No	399	c-a	US (Africa)	[146]
	Xq13.2-q21.1	CYSLTR1	927T/C	Yes	42	c	Spain	[12]
8	8p23.1	DEFB1*	-2266T/C, -1241T/G 668C/G, 692A/G, 1654G/A	Yes	631	c-a	Korea	[240]
				Yes	59	c-a	Mexico	[376]
9	9q32-q33	TLR4*	T399I	No	82	c	Netherlands	[371]
				No	129	a	Germany	[350]
				No	275_f	c	Germany	[522]
				Yes	78	a	Germany	[1]
			rs4986790	No	82	c	Netherlands	[371]
				No	129	a	Germany	[350]
				No	275_f	c	Germany	[522]
				Yes	78	a	Germany	[1]
			rs2770150	Yes	82	c	Netherlands	[371]
				No	275_f	c	Germany	[522]
10	10p15	GATA3*	rs2275806, rs444762	Yes	894	c	UK	[13]
	10q11.2	MBL2*	first exon A/O	Yes	131	c	Brazil	[70]
11	11p13	BDNF*	270C/T	Yes	160	a	China	[293]
			196G/A	No	160	a	China	[293]
				Yes	60	a, 1^{st}	China	[293]
	11p15.5	TOLLIP*	-526C/G	Yes	317	c-a	Germany	[421]
	11q12.3-q13.1	SCGB1A1*	38A/G	Yes	51	a	Denmark	[62]
	11q13	GSTP1	Ile105Val	Yes	34	c	Taiwan	[509]
				Yes	124	c	Korea	[97]
				Yes	126	c	Russia	[502]
				Yes	117	c	Russia	[413]
		MS4A2*	RsaI-in2*2, RsaI-ex7*1	Yes	$\underline{148}_{2f}$	c	US	[105]
	11q13.5	C11orf30	rs7927894	No	194	c-a	Japan	[344]
				Yes	511	c	Ireland	[356]
				Yes	270_f	c-a	Germany	**G [129]**
				Yes	$\underline{3576}_3$	c-a	Europe	**G [129]**

	11q22.2-22.3	IL18*	-137G/C	Yes	67	-	Poland	[481]
				No	160	a	Japan	[234]
				Yes	225	a	Germany	[347]
			113T/G, 127C/T, 133C/G	Yes	225	a	Germany	[347]
			rs795437	Yes	646	c-a	Korea	[241]
	11q23	IL10RA	S138G	Yes	25	-	Egypt	[208]
12	12q12-q13	TIMELESS*	5383_5397del	Yes	112	-	Korea	[71]
			157insMTTTVP	Yes	93_f	c	Australia	[364]
				No	30_f	c	Asia	[364]
	12q14	IFNG*	874T/A	Yes	25	-	Egypt	[209]
13	13q14.2	PHF11*	rs2247119, rs1046295	Yes	111_f	c	Australia	[217]
14	**14q11.2**	**CMA1***	**BstXI**	**META-ANALYSIS**				**[Table 3.2, p. 42]**
15	15q22.33	SMAD3*	rs4147358	Yes	111_f	c-a	Japan	[359]
				Yes	380	c-a	Japan	[359]
16	16p12.1-p11.2	IL4R*	-3112C/T	Yes	101	c-a	Japan	[197]
				No	74	c-a	Germany	[346]
			-1803T/C, -327C/A, -326A/C, -186G/A	Yes	101	c-a	Japan	[197]
			I50V	Yes	762	c	US	[38]
				No	207_f	c	US	[185]
				No	74	c-a	Germany	[346]
				No	302	a	Japan	[468]
				No	27	a	Japan	[351]
			Q551R	No	94	c-a	China	[79]
				No	207_f	c	US	[185]
				No	74	c-a	Germany	[346]
				Yes	245	c	UK	[60]
				No	302	a	Japan	[468]
				Yes	27	a	Japan	[351]
				Yes	7	c-a, sev	US	[180]
			S761P	No	207_f	c	US	[185]
				Yes	14	c-a, int	Germany	[346]
				No	60	c-a, ex	Germany	[346]
				No	27	a	Japan	[351]
	16q21	NOD2*	R702W	Yes	392	c-a	Germany	[295]
			2722G/C	Yes	330	c	Germany	[225]
17	17q11-q21	CCL3*	954C/T, 1245A/G, 1728C/G, 1771A/G	Yes	39	-	Japan	[540]
	17q11.2-q12	CCL5	-401G/A	Yes	389	c-a	Japan	[466]
				Yes	62	-	Japan	[22]
				No	128	c	Hungary	[255]
				Yes	188	c	Germany	[333]
			-28C/G	No	128	c	Hungary	[255]
				Yes	389	c-a	Japan	[466]
	17q21.1-q21.2	CCL11*	-426C/T	No	140	c-a	Japan	[487]
				Yes	68	c, ex	Italy	[398]
				No	62	c, int	Italy	[398]
	17q25.3	SOCS3*	rs12952093, rs4969170	Yes	406_f	c	Sweden	[119]
				Yes	328	c	Sweden	[119]
				No	187	a	UK	[119]
18	18q11.2	HRH4	ss142022671, ss142022677, ss142022679	Yes	301	c-a	China	[549]
19	19p13.3	TBXA2R	795C/T	No	360	c-a	Japan	[467]
				>Yes	89	c-a, e	Japan	[467]
	19p13.1	IL12RB1*	-111A/T, -2C/T	Yes	382	c-a	Japan	[463]
			IVS12 +1266T/C	Yes	631	c-a	Korea	[328]
	19q13.1	TGFB1*	R25P	Yes	68	c	UK	[11]
	19q13.4	KLK7	AACCins	No	99	c-a	France	[198]
				Yes	103	c-a	UK	[493]
	19q13.42	NLRP12	in9 T	Yes	392	c-a	Germany	[295]
20	20p13	ADAM33*	rs2853209	Yes	140	c	Japan	[306]
22	22q11.23	GSTT1	null allele	No	145	c-a	Korea	[92]
				No	34	c	Taiwan	[509]
				No	124	c	Korea	[97]

	Yes	126	c	Russia	[502]

Chr, chromosome; Locus, as published by the *NCBI*; Gene, given by its 'Official Gene Symbol' (aliases, gene name and location provided in the List of Genes); Variant, given by its base number (*GenBank*) or SNP ID (*NCBI SNP database*); Ass, states if an association was found or not; Size, sample size given by the number of cases (or families $_f$); Diff, differences of the study populations due to age (i, infants; c, children; a, adults; a-c, all ages) and/or disease characteristics (ex, extrinsic; int, intrinsic; sev, severe; 1^{st}, first degree atopic relatives; eos, blood eosinophilia; e, very high IgE level); Country, where the study populations reside; Ref, reference; *, these genes show both positive and negative reports for deviating variants; $_f$, family study; $\underline{100}_{2/3}$, sample consisting of 2 or 3 subsamples; G, this reference is a genome-wide association study.

A.2. Negative reports for atopic eczema

Table A.2.: Genetic variants without evidence of association with atopic eczema

Chr	Locus	Gene	Variant	Ref
1	1p31.3-p31.2	IL12RB2	17046A/G (rs12131065), 11759C/T, 9031G/T, 4935A/G, IVS2 383C/T, IVS3 + 146A/G, S238S, IVS9 7A/G, T643T	[328]
	1p13.1	NGF	rs11102930, rs7530686, rs7555016, rs6678788, rs910330, Ala35Val	[187]
	1p32-p31	VCAM1	rs1041163	[185]
	1q21	IVL	3'UTR	[449]
		LOR	Promoter, exon 1, 3'UTR	[449]
		PGLYRP3	Promoter, exon 3	[449]
		S100A1	Promoter, intron 1, intron 2	[449]
		S100A2	Promoter, exon 3	[449]
		S100A3	Promoter	[449]
		S100A4	exon 2	[449]
		S100A5	intron 3	[449]
		S100A6	Promoter	[449]
		S100A7	Promoter	[449]
		S100A8	Promoter	[449]
		S100A9	3'UTR	[449]
		S100A10	3'UTR, intron 2, promoter	[449]
	1q21.3	S100A14	3'UTR	[449]
		LCE3C/B	deletion	[33]
		FLG*	E2422X, Q2417X, R4307X, 7945delA	[294]
			rs11582620, rs11586114, rs1933064, rs3814299	[126]
		HRNR*	rs877776	[356]
			exon 3	[449]
		LCE3A	Promoter	[449]
		LCE5A	Promoter	[449]
	1q21-q22	SPRR1A	Promoter, exon2	[449]
		SPRR1B	intron 1	[449]
	1q22-q25	SELP	rs6131, rs6133	[185]
		SELE	rs5361	[185]
	1q23	FCER1A*	-315C/T, rs2251746	[339, 519]
			rs3845625, rs2511211, rs10489854, rs2494262, rs12565775, rs2427824, rs2427837	[519]
		FCGR2A	131 H/R	[369]
	1q31-q32	IL10	-1082G/A	[444, 79, 394, 11]
			-592A/C	[444, 79]
			rs1800872, rs3021097, rs1800896	[185]
	1q42-q43	AGT	M235T	[192]
	1q44	NLRP3	rs35829419, rs10754558, rs10802501	[375]
2	2p22-p21	NLRC4	Promoter	[295]
	2q12	IL1RL1*	744C/A, 2992C/T, 5283G/A, 5860C/A, 11147C/T	[432]
	2q14	IL1A	-899T/C	[185]
		IL1B	+3953 T/C	[380, 394]
			-511 T/C	[394]
			rs16944, rs1143634	[185]
	2q14.2	IL1RN	intron 2	[394]
	2q33	CTLA4*	rs5742909, rs231775	[185]
	2q35	CXCR1	3047C/T	[327]
		CXCR2	L262L, -1945T/C	[327]
3	3p26-p24	IL5RA*	rs17026903, 3806681, 35428885, 17881144, 6771148, 9831572, 2290610, 334809, 3804797, 17882210, 340808, 340830	[327]
			rs2290608	[185]
	3p24	CCR4	1014C/T	[490]
			rs7632357, rs2228428, rs6807638	[186]
	3p21.31	CCR2	rs1799864	[185]
		CCR5	rs333, rs1799987	[185]

	3p21.3	CCR3	51T/C	[489]
			rs5742906	[185]
		TLR9*	- 1486C/T	[350, 348]
			1174G/A, 2848G/A	[348]
	3q21	CSTA*	162T/C, -190T/C	[494]
	3q22.1	COL6A5*	rs1349747, rs1869319, rs1453243, A36624476, rs7628563, rs1566136, rs322113, rs322115, rs819091, rs7624712	[442]
	3q25.33-q26	IL12A	IVS1 +225A/G, IVS2 798A/T, 3437A/T	[328]
4	4p14	TLR1	rs5743618, rs5743613	[350]
		TLR6	rs5743810	[188]
	4q12-q13	GC	rs7041, rs4588	[185]
	4q13-q21	IL8	rs4073	[327]
	4q24	NFKB1	-94delATTG, rs1599961, rs230526, rs230491, rs3774963, rs4698863	[186]
	4q26-q27	IL2*	rs3087209	[95]
	4q31	IL15	rs3806798, rs1519551, rs2322262, rs1493012, rs2254514	[95]
	4q32	TLR2*	rs4696480	[350, 522]
			rs3804099, rs3804100	[522]
	4q34.1-q35.1	IRF2*	921G/A, 1739(ATCCC)8<6, -829C/T, -684C/T	[336]
5	5p13	IL7R*	rs10213865, rs1389832, rs10058453	[146]
			rs11567685, rs1494555, rs3194051	[184]
	5q22.1	TSLP*	rs1898671, rs2416259	[146]
	5q31	IL13*	329G/A	[305, 185]
			rs1295686	[13, 185]
			rs2066960, rs1295685	[13]
			704A/C, 1103C/T	[488]
		RAD50*	rs2069812, rs6884762, rs17772565, rs17772583, rs2214370	[519]
	5q31.1	CD14*	rs2569191, rs5744455, rs2563298	[371]
			rs2569191, rs5744455	[440]
		CSF2*	545G/A	[174]
			rs25882	[185]
		IL4*	-34C/T	[121]
			33T/C	[79]
		IL5*	rs2706400	[327]
		IL9	rs2069885	[185]
		TCF7	rs5742913	[185]
	5q31.1-q33.1	IL12B*	4237G/A, 4496A/G, 4510G/A	[79]
			6110T/C, 1340G/C, 671T/G, IVS2 912G/A (rs2569254), IVS4 + 314C/A	[328]
	5q32	SPINK5*	Asp106Asn	[337]
			Asp386Asn	[337, 508, 233]
			Glu825Asp	[337]
	5q33.3	HAVCR2	rs4704853, rs1036200, rs1036199, rs4704846	[364]
		TIMD4	rs1363232, rs4704727, rs7717984, rs7700944, rs1345616, rs77332745, rs10070224	[364]
	5q35	LTC4S	rs730012	[185]
6	6p24.1	EDN1	intron 4, position 8000	[192]
		HLA-DMA	0101, 0102, 0103	[262]
		HLA-DMB	0101, 0102, 0103	[262]
		HLA-DRB1	0101, 0401, 0403, 0405, 0406, 0410, 1101, llNew, 1201, 1202, 1401, 1403, 1405, 1406, 0701, 0802, 0803, 0901	[411]
			1302, 1501, 1502, 1602	[411, 410]
		HLA-DQB1	0201, 0301, 0302, 0303, 0401, 0402, 0501, 0502, 0503, 0601, 0602, 0604	[410]
		HLA-DPB1	0201, 0202, 0301, 0401, 0402, 0501, 0601, 0901, 1301, 1401, 1601, 1701, 1901	[410]
		LTA	rs909253	[185]
		PSMB9	R, H (60)	[272]
		PSMB8	A, B, C, D (3911, 3912, 4069)	[272]
		TAP2	379, 565, 665	[264]
			687	[264, 263]
		TNF	-308 G/A	[394, 79, 380, 185]
			-238 G/A	[394, 79, 185]

			-857C/T, -863C/A, -1031T/C	[79]
	6p12	IL17F	7488T/C	[431]
	6q21	SMPD2	-318C/T, -89G/A, 8C/T, 276A/C, 716G/C, 1231C/T, 1898G/A, 2080C/T	[242]
7	7p21	IL6	-174C/G	[394, 185]
			rs1800796	[185]
	7p15-p14	NOD1*	Prom/ In1 / In2 / Ex6 / In6 / In11 SNPs	[295]
			rs3020207, rs2075818, rs2235099, rs2075821, rs5743368	[521]
				[521]
	7p14.3	NPSR1	rs323917, rs324377, rs324384, rs324396, rs74037, SNP546333	[118]
			rs323922	[118, 443]
	7q22	EPO	rs11652709, rs3785496	[367]
	7q36	NOS3	rs1800779, rs1799983	[185]
X	Xp22	TLR8*	rs5741883, rs3764879, rs3764880, rs5744077, rs2159377	[313]
	Xp22.3	TLR7*	rs5743781, rs864058	[313]
	Xq24	IL13RA1	R110Q	[346]
				[305]
8	8p23	DEFA4	G-6298C, T-5144G, G-4477C, T-2576C, G-1780A, T-668C, T-446A, G85G, G2277A	[240]
	8pter-p21	DEFA5	G-2819A, G-1027C, G-427A, T69T, G3357A	[240]
		DEFA6	G-4844A, G-3145A, C-79A, IVS1-268G/C, G957A, T1953G, G2844A	[240]
	8p23.2-p23.1	DEFB1*	-44C/G	[424, 240]
			-20G/A, -52G/A	[424]
			IVS1 + 2262T/C, IVS1 - 3050T/A	[240]
			1836A/G	[376]
	8p22	NAT2	481C/T, 590G/A	[299, 51]
			857G/A	[51]
9	9q32-q33	TLR4*	rs6478317, rs1927911	[371, 522]
			rs10759932, rs11536878, rs11536889	[371]
			rs2149356, rs7873784, rs1927906	[522]
	9q33-q34	C5	rs17611	[185]
10	10p15	GATA3*	rs4143094, rs2229359, rs406103, rs1058240, rs379568	[13]
	10p15-p14	IL2RA	rs12722489, rs2104286, rs11256369, rs7076103	[184]
	10q11.1	CXCL12	rs1801157	[185]
	10q11.2-q21	MBL2*	Gly54Asp	[172]
11	11p15.5	TOLLIP*	rs5743867, rs11042484,rs3750920, rs5744015 , rs3750919	[421]
	11p13	BDNF*	Val66Met	[187]
	11q12.3-q13.1	SCGB1A1*	rs3741240	[185]
	11q13	MS4A2*	6886G/A	[305]
			rs1441586, rs569108	[185]
	11q22.2-22.3	IL18*	132A/G	[347]
			rs4937113, rs5744247	[241]
	11q24.2	TIRAP*	rs8177374	[350]
12	12q12-q13	TIMELESS*	5509_5511delCAA	[71]
			- 1454, rs6420075, rs1809941, rs1553316	[364]
	12q13	STAT6	2964G/A	[465, 464]
			13R-17R	[79]
			rs12368672	[519]
	12q13.11	VDR	rs2228570, rs1544410	[185]
	12q14	IFNG*	intron 1	[79]
	12q14.3	IRAK3	rs2870784, rs1177578, rs2141709, rs11465955, rs1624395, rs1370128	[36]
13	13q14	SETDB2	rs2057413, rs2077848, rs4941643	[217]
	13q14.2	PHF11*	rs2031532, rs2274276	[217]
14	14q11.2	CMA1*	rs195692, rs5244, rs5246, rs5247, rs5248, rs5250	[523]
	14q24-q31	RNASE2	rs2013109, rs10132319	[367]
		RNASE3	rs17792481, rs2073342, rs2233860	[367]

15	15q22.33	SMAD3*	rs16950553, rs11632964, rs11635145, rs12901071, rs16950556, rs2083194, rs12907997, rs16950561, rs1465841, rs9972423, rs4776890, rs2118611, rs1438386, rs7163381, rs4776892, rs11631254, rs1992215, rs6494633, rs12915039, rs745103, rs12439792, rs893473, rs12441344, rs4601989, rs1065080, rs2289259, rs3784681, rs6494636, rs3743343	[359]
	15q24.3	BCL2A1	-1182C/G, 202G/T, 303A/G	[156]
	15q26.3	IL16	-295T/C	[393]
16	16p12.1-p11.2	IL4R*	Q375A	[79, 346, 468, 351, 185]
			C406R	[79, 346, 351, 185]
			S478P	[346, 185]
			Ser411Leu	[351]
			L389L	[79, 185]
			S503P	[79]
			N142N, Promoter(-3223)	[185]
	16q13	CCL17	-431C/T	[483, 425]
			2134C/T, 2037G/A	[425]
	16q21	NOD2*	2104C/T, 3020insC	[225]
			rs5743266, rs2067085, rs2066842, rs2066844, rs2066845, rs5743291, rs1077861, rs3135500	[520]
17	17p13.2	NLRP1	rs12150220, rs2670660	[375]
			Promoter	[295]
	17q11.2-q12	CCL2	-2518G/A	[255]
		NOS2	rs1137933	[185]
	17q11-q21	CCL3*	954C/T, 1245A/G, 1728C/G, 1771A/G	[540]
	17q21.1-q21.2	CCL11*	-384A/G, 67G/A	[487, 398]
			rs3744508, rs4795895	[185]
	17q23.3	ACE	insertion/ deletion genotype	[192]
	17q25	RUNX1-binding-site	rs734232	[196]
	17q25.3	SOCS3*	rs4969168	[119]
18	18q23	MBP	rs490358, rs3741098	[367]
19	19p13	CD209	rs11465360, rs11465413, rs11465421, rs2287886, rs4804803, rs4804804, rs7252229, rs735239, rs735240, rs7359874, rs8112555	[372]
	19p13.3-p13.2	C3	rs10410674, rs366510, rs10402876, rs423490	[377]
			rs2230199	[185]
		ICAM1	rs5491, rs1799969	[185]
	19p13.1	IL12RB1*	4124G/A, IVS2 117T/C, M365T, IVS15 67G/A, 2410T/A, 3733T/C	[328]
	19q13.1	TGFB1*	L10P	[11]
			rs1800469	[185]
20	20pter-p12	PDYN	Promoter H/L	[157]
			-946C/G	[157]
	20p13	ADAM33*	rs597980, rs628977, rs2280090, rs2280091, rs2787094, rs528557	[306]
	20q11.22-q11.23	ITCH	44663G/A, 46586A/G, 55719C/T, 68490G/A, 85923C/T, 113984T/C, 114128T/C, 114274A/G	[34]

Chr, chromosome; Locus, as published by the *NCBI*; Gene, given by its 'Official Gene Symbol' (aliases, gene name and location provided in the List of Genes); Variant, given by its base number (*GenBank*) or SNP ID (*NCBI SNP database*); Ref, references; *, these genes show both positive and negative reports for deviating variants; Note: negative reports for marker SNPs of genome-wide association studies were not included;

B. Association studies on genetic predispositions to psoriasis

B.1. Positive reports for psoriasis

Table B.1.: Genetic variants providing evidence of association with psoriasis in at least one published study

Chr	Locus	Gene	Variant	Ass	Size	Clinic	Country	Ref
1	1p36.3	MTHFR	677C/T	Yes	410	P	Czech Republic	[496]
				No	310	P	Austria	[514]
	1p36.11	IL28RA	rs4649203	Yes	$\underline{6520}_2$	P	Europe	**G [453]**
	1p31.3	**IL23R***	**rs7530511**	**META-ANALYSIS**				**[Table 4.10, p. 116]**
			rs11209026	**META-ANALYSIS**				**[Table 4.10, p. 116]**
			rs2201841	No	250_f	P	Finland	[117]
				Yes	$\underline{6407}_2$	PPA	Eur, US, Can	**G [318]**
				Yes	$\underline{496}_2$	PA	Canada	[384]
				No	819	P	UK	**G [65]**
	1p31.3-p31.2	IL12RB2	rs12131065	Yes	810	P	US	**G [287]**
	1p13.3	GSTM1	null allele	Yes	327	P	Germany	[396]
				No	100	P1	Germany	[395]
	1p13.3-p13.1	**PTPN22***	**rs2476601 (R620W)**	**META-ANALYSIS**				**[Table 4.5, p. 82]**
			rs3789604	Yes	2047	P	US	[283]
				Yes	900	P1	UK	[438]
			rs1217414	No	1448	P	US	[283]
				Yes	900	P1	UK	[438]
	1q21	IVL	rs6661932, rs4845497, rs2879485	Yes	494	P	Singapore	[86]
			rs16834751, rs11205132, rs2229496, rs913996	No	494	P	Singapore	[86]
				>Yes	360	P1	Singapore	[86]
		Intergenic	rs11205128	Yes	494	P	Singapore	[86]
			rs2339396, rs4845501	No	494	P	Singapore	[86]
				>Yes	360	P1	Singapore	[86]
		PGLYRP3*	rs821421	No	282	P	US	[457]
				Yes	101_f	P	US	[457]
		PGLYRP4*	rs3006448, rs3006450, rs3006452, rs3006457, rs2916205	No	282	P	US	[457]
				Yes	101_f	P	US	[457]
	1q21.3	**LCE3C/B**	**deletion**	**META-ANALYSIS**				**Riveira-M. 2010 [399]**
			rs4112788	**META-ANALYSIS**				**Riveira-M. 2010 [399]**
			rs4085613	Yes	1057	PA	UK, Ireland	[48]
				Yes	$\underline{6860}_3$	P	China	**G [557]**
			rs10888502, rs4845456	Yes	1354	P	Germany	[199]
				No	650	PA	Germany	[200]
		FLG*	rs1858483	Yes	126_f	P	France	[360]
			rs11584340	Yes	314	P	Taiwan	[74]
		LCE1A	rs4845325	No	494	P	Singapore	[86]
				>Yes	360	P1	Singapore	[86]
		LCE1C	rs6701216	Yes	810	P	US	**G [287]**
				No	1057	PA	UK, Ireland	[48]
		LCE2A	rs7543194	Yes	494	P	Singapore	[86]

		LCE3A	rs1011297	Yes	494	P	Singapore	[86]
			rs4845454, rs1886734	Yes	$\underline{6860}_3$	P	China	**G [557]**
		LELP1	rs10494291, rs10494292	Yes	494	P	Singapore	[86]
		PRR9	rs10494292, rs10788861, rs1410859, rs1410860, rs12127862, rs10888541, rs4845342	Yes	494	P	Singapore	[86]
		SMCP	rs3737861	No	494	P	Singapore	[86]
				>Yes	360	P1	Singapore	[86]
	1q21-q22	SPRR2C	rs509194	Yes	494	P	Singapore	[86]
		SPRR2F	rs1500941	Yes	494	P	Singapore	[86]
				No	255_f	P1	Finland	[226]
		SPRR2G	rs428913	Yes	494	P	Singapore	[86]
	1q24	Intergenic	rs12035082	Yes	1256	P1	UK	[530]
	1q31-q32	**IL10***	**-1082A/G**	**META-ANALYSIS**				**[Table 4.4, p. 78]**
			-2763A/C	Yes	139	P	Thailand	[533]
	1q32	IL20*	-1723C/G	Yes	340	P	China	[87]
			1380A/G	Yes	43	PPP	Estonia	[248]
				No	154	P	Estonia	[246]
			-1053T/G, 3978T/C	No	43	PPP	Estonia	[248]
				Yes	154	P	Estonia	[246]
	1q32.2	IL19*	rs2243188	Yes	43	PPP	Estonia	[248]
				Yes	254	P	Estonia	[250]
	1q43	RYR2	rs2485558	Yes	$\underline{3218}_2$	P	Ger, US, Can	**G [120]**
2	2p13-p12	REL	rs702873	Yes	$\underline{6520}_2$	P	Europe	**G [453]**
	2q12-q14.1	IL1F7	rs3811047	Yes	212	PA	Canada	[387]
	2q14	IL1A*	-889C/T	No	212	PA	Canada	[387]
				No	170	P	Taiwan	[77]
				No	102	PA	Taiwan	[77]
				Yes	140	PA	UK	[388]
				No	226	PA	Canada	[370]
		IL1B*	-511C/T	No	170	P	Taiwan	[77]
				No	102	PA	Taiwan	[77]
				No	156	P1	Germany	[392]
				Yes	75	P2	Germany	[392]
			-31C	No	170	P	Taiwan	[77]
				No	102	PA	Taiwan	[77]
				Yes	212	PA	Canada	[387]
	2q14.2	**IL1RN**	**VNTR (intron2)**	**META-ANALYSIS**				**[Table 4.3, p. 74]**
			rs397211	Yes	$\underline{6407}_2$	PPA	Eur, US, Can	**G [318]**
			rs315934	Yes	126_f	P	France	[360]
	2q24	IFIH1	rs17716942	Yes	$\underline{6520}_2$	P	Europe	**G [453]**
			rs35667974, rs10930046	Yes	2098	P	US	[282]
	2q32.2-q32.3	STAT4	rs7574865	Yes	163	PA	Crete	[555]
3	3p25	PPARG	rs1801282	Yes	251	PA	Canada	[54]
	3p24	Intergenic	rs6809854	Yes	$\underline{6520}_2$	P	Europe	**G [453]**
	3p21.3	CX3CR1	hCV-11578468, c_5687_1	Yes	281	P	UK	[374]
	3p21.31	CCR2	-I64V	No	382	P	Spain	[445]
				Yes	81	PA	Spain	[445]
	3q21	CSTA	162T/C	Yes	107	P	UK	[495]
	3q21.2	SLC12A8	rs658971, rs2137599	Yes	126_f	P	France	[360]
			ss35527511, ss35527513, rs9813946, rs9831295, rs1554241, rs651630	Yes	375	P	Germany	[203]
				No	210_f	P	Germany	[203]
			rs2228674	Yes	210_f	P	Germany	[203]
			BES2, IAP8, EC2	Yes	195_f	P	Sweden	[181]
4	4q24	NFKB1	-94ins/del	Yes	519	P	China	[280]
				No	224	PA	Canada	[58]
	4q26-q27	IL2	rs2069762	Yes	114	P	Korea	[244]
	4q27	IL2-IL21	rs13151961, rs7684187, rs6822844, rs6840978	Yes	576	PA	UK	**G [287]**
				No	810	P	US	**G [287]**
	4q31	IL15*	g.96516A/T	No	1448	P	US	[283]
				No	661	P1	UK	[436]
				No	311	P	Austria	[516]

				Yes	632	P	China	[558]
5	5q15	ERAP1	rs27524	Yes	$\underline{6520}_2$	P	Europe	**G [453]**
			rs151823	Yes	$\underline{8312}_4$	P	China	**G [458]**
				No	$\underline{3889}_3$	P	Germany, US	**G [458]**
	5q31	**IL13**	**rs20541**	**META-ANALYSIS**				**[Table 4.8, p. 102]**
			rs848	Yes	178	PA	US	[114]
				No	437	P	US	[114]
			rs1800925	Yes	$\underline{225}_2$	PA	US	[114]
				No	$\underline{679}_2$	P	US	[114]
				Yes	1448	P	US	[281]
		SLC22A4/5*	rs2631367	No	264_f	P	Sweden	[141]
				Yes	472	PA	UK	[183]
				No	218	P1	UK	[183]
		SLC22A5	rs274559	Yes	45_f	P	France	[360]
	5q31.1	SLC22A4	rs11568506	Yes	1448	P	US	[281]
		IL4*	-590C/T	Yes	114	P	Korea	[244]
				No	170	P	Taiwan	[77]
				No	102	PA	Taiwan	[77]
				No	84	P	UK	[106]
	5q31-q32	ADRB2*	Arg16Gly	Yes	32	P, sp	Turkey	[362]
				No	18	P, fa	Turkey	[362]
	5q31.1-q33.1	**IL12B***	**rs3212227**	**META-ANALYSIS**				**[Table 4.9, p. 106]**
			rs6887695	**META-ANALYSIS**				**[Table 4.9, p. 106]**
			rs2569253	Yes	170	P	Taiwan	[77]
				No	102	PA	Taiwan	[77]
			rs7709212	Yes	$\underline{6860}_3$	P	China	**G [557]**
				Yes	837	P	UK	**G [65]**
			rs3213094	Yes	2622	P	UK, Ireland	**G [453]**
				Yes	$\underline{6860}_3$	P	China	**G [557]**
			rs2082412	Yes	$\underline{6407}_2$	PPA	Eur, US, Can	**G [318]**
			rs10045431	Yes	837	P	UK	**G [65]**
			rs12188300	Yes	2370	PPA	Europe	**G [206]**
			rs2546890, rs953861	Yes	$\underline{3218}_2$	P	Ger, US, Can	**G [120]**
	5q32-q33.1	TNIP1	rs1023995	Yes	2622	P	UK, Ireland	**G [453]**
			rs17728338	Yes	$\underline{6407}_2$	PPA	Eur, US, Can	**G [318]**
	5q33.1	TNIP1-ANXA6	rs3762999, rs999556	Yes	$\underline{7773}_3$	P	China	**G [458]**
		IRGM	rs1000113	Yes	1256	P1	UK	[530]
	5q35.1	PTTG1	rs2431697	Yes	$\underline{5749}_2$	P	China	**G [458]**
				No	$\underline{4428}_4$	P	China, Ger, US	**G [458]**
	5q35.3	FLT4*	rs3776413, rs307823	Yes	243	P	Korea	[273]
6	6p22.3	CDKAL1	rs6908425	Yes	2047	P	US	[283]
				Yes	1256	P1	UK	[530]
	6p21.3	AGER*	2184A/G	Yes	130	P	Czech Republic	[499]
			G82S	No	130	P	Czech Republic	[499]
				Yes	142	P	Czech Republic	[228]
		C2	2	No	79	P	Japan	[325]
				Yes	230	P	Germany	[110]
		C4A*	3, 4	Yes	79	P	Japan	[325]
		C4B*	1, 2	Yes	79	P	Japan	[325]
		c6orf10	rs2073048	Yes	$\underline{2498}_2$	P	US, China	**G [132]**
		CBF	F	Yes	79	P	Japan	[325]
				Yes	230	P	Germany	[110]
			SO7	Yes	230	P	Germany	[110]
		CCHCR1*	**WWCC**	**META-ANALYSIS**				**[Table 4.21, p. 180]**
			251T	Yes	59	P	Israel	[303]
				Yes	100	P	Finland	[17]
			256T	Yes	95	P	Spain	[304]
				No	74	PA	Spain	[304]
			269T	No	77	P	Europe	[503]
				Yes	100	P	Finland	[17]
			325T, 2327G	Yes	145	P2	UK	[6]
				No	281	P	Germany	[267]
				No	375	PA	Germany	[267]
				Yes	134	PG	UK	[16]
				No	$\underline{156}_2$	PPP	UK, Sweden	[16]

		Yes	419_f	P	Eur, India	[19]
	307T, 1723T	Yes	134	PG	UK	[16]
		No	$\underline{156}_2$	PPP	UK, Sweden	[16]
		Yes	419_f	P	Eur, India	[19]
	421T	Yes	100	P	Finland	[17]
	492G, 1249T, 1285T	Yes	134	PG	UK	[16]
		No	$\underline{156}_2$	PPP	UK, Sweden	[16]
	771C, 1911G	Yes	419_f	P	Eur, India	[19]
	-386T, -404T, -1802T, -2406G	Yes	115	P	Taiwan	[81]
CDSN*	**+619T**	**META-ANALYSIS**				**[Table 4.15, p. 130]**
	+1243C	**META-ANALYSIS**				**[Table 4.15, p. 130]**
	+722T	No	178	P	Taiwan	[76]
		>Yes	92	P1	Taiwan	[76]
		No	93	P1	Thailand	[402]
		No	105	P	Taiwan	[82]
		Yes	232_f	P	Sweden	[123]
	+971T	No	178	P	Taiwan	[76]
		>Yes	92	P1	Taiwan	[76]
		Yes	171	P	UK	[63]
		No	93	P1	Thailand	[402]
	+1215G	Yes	178	P	Taiwan	[76]
		No	43	P	Japan	[8]
		Yes	153_f	P	UK	[8]
		No	$\underline{436}_2$	PA	Canada	[57]
		No	145	P2	UK	[6]
		No	93	P1	Thailand	[402]
		No	147	P	Italy	[358]
	+1236T	No	178	P	Taiwan	[76]
		No	59	P	Israel	[303]
		No	43	P	Japan	[8]
		Yes	153_f	P	UK	[8]
		No	436	PA	Canada	[57]
		No	145	P2	UK	[6]
		No	147	P	Italy	[358]
		No	235	P	UK	[472]
HCP5	rs2395029	Yes	810	P	US	**G [287]**
HLA-Genes*		**SUMMARY**				**[Table 4.1, p. 56]**
HLA-B*	**B*57**	**META-ANALYSIS**				**[Table 4.22, p. 184]**
HLA-C*	**w*0602**	**META-ANALYSIS**				**[Table 4.25, p. 189]**
	rs12191877	Yes	472	P	Ger, US, Can	**G [120]**
		Yes	1139	P	China	[132]
		Yes	$\underline{6407}_2$	PPA	Eur, US, Can	**G [318]**
	rs1265181	Yes	5067	P	China	[562]
		Yes	2519	P	China	[561]
		Yes	$\underline{1139}_2$	P	China	**G [557]**
	rs10484554	Yes	2622	P	UK, Ireland	**G [453]**
		Yes	810	P	US	**G [287]**
	rs3131000, rs3130559	Yes	150	P	France	[434]
	rs3134792	Yes	318	P	UK	**G [65]**
	rs13191343	Yes	2370	PPA	Europe	**G [206]**
Intergenic	**SNP n.9**	**META-ANALYSIS**				**[Table 4.19, p. 175]**
	SNP n.7	No	59	P	Israel	[303]
		No	242_f	P	US	[177]
		Yes	115	P	Taiwan	[81]
		Yes	134	PG	UK	[16]
		Yes	77	P	Europe	[503]
LTA*	Nco I	Yes	103	P	Korea	[243]
		Yes	49	PPP	Japan	[171]
		Yes	142	P	Czech Republic	[500]
		No	70	P	Finland	[211]
	+252A	Yes	375	P	Germany	[391]
		No	376	PA	Germany	[391]
		No	147	PA	Ireland	[24]
MICB	CA-22	Yes	81	PA	Spain	[153]

	PSORS1C1*	39604C/T	No	$\frac{305}{2}$	PA	Canada	[382]
			Yes	87	P	Sweden	[194]
		rs3815087	Yes	242	P	US	[177]
		39706C/T, 39709C/T, 39610G/A, 26680C/T	Yes	87	P	Sweden	[194]
	PSORS1C2*	26276T/C	Yes	87	P	Sweden	[194]
		988C/G	No	116	P	China	[83]
			>Yes	70	P1	China	[83]
	RXRB	+140A/T	Yes	39	PG	Czech Republic	[497]
			No	44	PG	Czech Republic	[497]
			No	291	P	Czech Republic	[497]
	TAP1*	637	Yes	98	P	Korea	[379]
			No	142	P	Czech Republic	[500]
	TAP2*	665	Yes	98	P	Korea	[379]
	TNF*	**-308G/A**	**META-ANALYSIS**			**[Table 4.16, p. 150]**	
		-238G/A	**META-ANALYSIS**			**[Table 4.16, p. 150]**	
		-857C/T	**META-ANALYSIS**			**[Table 4.18, p. 172]**	
6p21.31	POU5F1*	B (HindIII)	Yes	59	P	Israel	[303]
			Yes	95	P	Spain	[304]
			No	74	PA	Spain	[304]
			Yes	95	P1	Spain	[152]
		A	No	59	P	Israel	[303]
		-166C, 77A, 144A, 347T, 1377T	Yes	174	P	China	[78]
6p21.33	**MICA***	**A9**	**META-ANALYSIS**			**[Table 4.12, p. 123]**	
		A4	No	100	PA	Czech Republic	[137]
			No	170	P	Taiwan	[77]
			No	102	PA	Taiwan	[77]
			Yes	58	PA	Croatia	[160]
			No	105	P	Taiwan	[82]
			No	52	PA	Israel	[151]
			No	300	P	China	[89]
			Yes	138	P	Korea	[93]
			No	45	P	Spain	[154]
			No	65	PA	Spain	[154]
		A5.1	No	100	PA	Czech Republic	[137]
			No	170	P	Taiwan	[77]
			No	102	PA	Taiwan	[77]
			No	105	P	Taiwan	[82]
			No	52	PA	Israel	[151]
			Yes	138	P	Korea	[93]
			Yes	300	P	China	[89]
			No	45	P	Spain	[154]
			No	65	PA	Spain	[154]
		A5, A6	No	100	PA	Czech Republic	[137]
			No	170	P	Taiwan	[77]
			No	102	PA	Taiwan	[77]
			No	58	PA	Croatia	[160]
			No	105	P	Taiwan	[82]
			No	52	PA	Israel	[151]
			No	300	P	China	[89]
			Yes	138	P	Korea	[93]
			No	45	P	Spain	[154]
			No	65	PA	Spain	[154]
		1*06	Yes	52	P1	Australia	[471]
	MICA-HLA-B	rs13437088	Yes	1359	P	US	**G [132]**
	PSORS1C3*	rs887468	Yes	178	P	Taiwan	[76]
		rs3871247, ss15721489, rs3871246	No	178	P	Taiwan	[76]
			Yes	218	P	Sweden	[195]
6p12	**VEGFA***	**+405G/C**	**META-ANALYSIS**			**Wu 2010 [537]**	
		+936C/T	Yes	258	PA	Canada	[55]
		-460C/T	No	154	P	Thailand	[534]
			Yes	117	P	Italy	[29]
			Yes	292	P1	UK	[548]

				No	160	P1	UK	[547]
			-152G/A	Yes	117	P	Italy	[29]
	6q21	TRAF3IP2	rs240993, rs458017	Yes	$\underline{6520}_2$	P	Europe	**G [453]**
			rs13210247, rs33980500	Yes	$\underline{6487}_2$	P	Ger, US, Can	**G [120]**
				Yes	2370	PPA	Europe	**G [206]**
			rs13196377, rs13190932	Yes	2370	PPA	Europe	**G [206]**
	6q22.33-q23.1	IL20RA*	rs1342642	Yes	548	P	Estonia	[249]
	6q23	TNFAIP3	rs610604	Yes	2622	P	UK, Ireland	**G [453]**
				Yes	$\underline{6407}_2$	PPA	Eur, US, Can	**G [318]**
	6q25.3	SOD2	1183C/T	Yes	52	PA	Taiwan	[544]
7	7p21	IL6	-174	Yes	46	P	Egypt	[429]
				No	78	P	Poland	[28]
				No	147	PA	Ireland	[24]
	7q36	NOS3	894G/T	Yes	109	P	Turkey	[428]
	7q36.2	DPP6	rs916514	Yes	$\underline{3218}_2$	P	Ger, US, Can	**G [120]**
X	Xp11.23	FOXP3*	-3279A/C, IVS9 +459A/G	Yes	524	P	China	[144]
	Xq28	IRAK1*	rs3027898	Yes	29	PA	Greece	[84]
8	8p22	NAT2*	481C/T	Yes	45	P, med	Russia	[254]
	8p23.1	DEFB	CNV (≥ 6)	Yes	$\underline{498}_2$	P	NL, Germany	[193]
	8p23.2	CSMD1	rs7007032, rs10088247	Yes	$\underline{7773}_3$	P	China	**G [458]**
				No	$\underline{4428}_4$	P	China, Ger, US	**G [458]**
9	9q34	TSC1	rs1076160	Yes	$\underline{6407}_2$	PPA	Eur, US, Can	**G [318]**
	9q34.3	RXRA*	A39526AA	Yes	163	P	Czech Republic	[497]
				No	130	P	Czech Republic	[497]
				No	83	PG	Czech Republic	[497]
11	11q22.2-q22.3	IL18	-137G/C	Yes	153	P	Japan	[234]
	11q24	MMP27	rs1939015	Yes	$\underline{3218}_2$	P	Ger, US, Can	**G [120]**
12	12q13	RPS26	rs12580100	Yes	$\underline{5895}_2$	P	Eur, US, Can	**G [455]**
	12q13.11	**VDR***	**ApaI**	**META-ANALYSIS**				**[Table 4.6, p. 86]**
			TaqI	**META-ANALYSIS**				**[Table 4.6, p. 86]**
			BsmI	**META-ANALYSIS**				**[Table 4.6, p. 86]**
	12q13.3	IL23A*	rs2066808	Yes	2622	P	UK, Ireland	**G [453]**
				Yes	$\underline{6407}_2$	PPA	Eur, US, Can	**G [318]**
			rs2066807	Yes	$\underline{6407}_2$	PPA	Eur, US, Can	**G [318]**
	12q14	IFNG	874A/T	Yes	78	P	Poland	[28]
			intron1	Yes	78	P	Poland	[28]
				No	114	P	Korea	[244]
				No	84	P	UK	[106]
				No	170	P	Taiwan	[77]
				No	102	PA	Taiwan	[77]
13	13q11-q12	GJB2	rs3751385	Yes	$\underline{8605}_4$	P	China, Ger	**G [458]**
				No	$\underline{3605}_3$	P	China, US	**G [458]**
	13q12-q14.11	LHFP-COG6	rs7993214, rs3812888	Yes	810	P	US	**G [287]**
	13q14-q21	HTR2A	-1438G/A	No	68	P1	Thailand	[404]
				Yes	38	P2	Thailand	[404]
14	14q13	NFKBIA*	rs8016947	Yes	$\underline{6520}_2$	P	Europe	**G [453]**
			rs2145623	Yes	$\underline{3218}_2$	P	Ger, US, Can	**G [120]**
		NFKBIA/ PSMA6	rs12586317	Yes	$\underline{5895}_2$	P	Eur, US, Can	**G [455]**
	14q32.33	IGH@	5*JH	Yes	22	P	Italy	[415]
				No	55	PA	Italy	[415]
15	15q21.2	TNFAIP8L3-USP8	rs3803369, rs4775912	Yes	810	P	US	**G [287]**
	15q24.1	CYP1A1	1A	Yes	321	P	Germany	[256]
			2A, 2C	Yes	321	P	Germany	[256]
				Yes	327	P	Germany	[396]
			4887C/A, 4889A/G	Yes	52	PA	Taiwan	[545]
16	16p12.1-p11.2	IL4R*	-326A/C, -186G/A	Yes	68	P	Japan	[142]
	16p11.2	FBXL19	rs10782001, rs12924903	Yes	$\underline{5895}_2$	P	Eur, US, Can	**G [455]**
	16q12.1	CYLD	rs4785452	Yes	126_f	P	France	[360]
			rs12925755	Yes	45_f	P	France	[360]
	16q13-q21	MMP2*	-790T/G	Yes	386	P	Czech Republic	[498]
			-735C/T	No	386	P	Czech Republic	[498]
				Yes	119	P	Czech Republic	[501]

	16q21	NOD2*	rs2076752	Yes	126_f	P	France	[360]
			rs2111235, rs8057341, rs17221417	Yes	45_f	P	France	[360]
			R702W	No	472	PA	UK	[183]
				No	148	P1	UK	[373]
				Yes	126_f	P	France	[360]
				No	281	P	Germany	[267]
				No	375	PA	Germany	[267]
				No	193	PA	Italy	[149]
				Yes	187	PA	Canada	[381]
				No	90	P	Italy	[43]
17	17q11.2-q12	CCL2	-2518	Yes	507	P	China	[511]
		NOS2	rs4795067	Yes	$\underline{5895}_2$	P	Eur, US, Can	**G [455]**
	17q23.3	**ACE**	**ins/del**	**META-ANALYSIS**				**[Table 4.7, p. 93]**
	17q24-q25	FDXR*	rs552432, rs899317	Yes	242_f	P	Europe	[176]
	17q25	GRIN2C	rs690578	Yes	242_f	P	Europe	[176]
	17q25.1	TMEM104*	rs2016126, rs939537	Yes	242_f	P	Europe	[176]
		CD300A	R111Q	Yes	242	P	US	[447]
		CD300LB	TREM5	Yes	242	P	US	[447]
		NAT9	rs12797, rs880827, rs3744208, rs2305214, rs878906, rs878907	Yes	242_f	P	Europe	[176]
		RUNX1-binding-site	rs734232	No	245	PA	Italy	[150]
				No	579_f	P1	Germany, US	[454]
				No	233_f	P	UK	[66]
				Yes	242_f	P	Europe	[176]
			rs745318	No	579_f	P1	Germany, US	[454]
				Yes	242_f	P	Europe	[176]
			rs895691	No	579_f	P1	Germany, US	[454]
				No	233_f	P	UK	[66]
				Yes	242_f	P	Europe	[176]
			rs8956692	Yes	242_f	P	Europe	[176]
		SLC9A3R1*	rs7420	No	245	PA	Italy	[150]
				No	233_f	P	UK	[66]
				Yes	242_f	P	Europe	[176]
	17q25.3	RAPTOR*	rs2019154	No	579_f	P1	Germany, US	[454]
				Yes	233_f	P	UK	[66]
			rs1564864	No	579_f	P1	Germany, US	[454]
				No	233_f	P	UK	[66]
				>Yes	116_f	P	UK	[66]
18	18q21.3	SERPINB8	rs514315	Yes	$\underline{7773}_3$	P	China	**G [458]**
				No	$\underline{4428}_4$	P	China, Ger, US	**G [458]**
19	19p13.3	KIR2DL5A	+	Yes	96	P	Japan	[460]
	19p13.2	SMARCA4	rs12983316	Yes	$\underline{6407}_2$	PPA	Eur, US, Can	**G [318]**
		TYK2	rs12720356, rs280519	Yes	$\underline{6520}_2$	P	Europe	**G [453]**
	19q13.4	KIR2DL2	+	No	102	PA	Taiwan	[77]
				Yes	366	PA	Canada	[302]
		KIR2DS1	+	No	102	PA	Taiwan	[77]
				Yes	116	PV	Poland	[292]
				Yes	96	PV	Japan	[460]
				Yes	366	PA	Canada	[302]
		KIR2DS2	+	No	102	PA	Taiwan	[77]
				Yes	366	PA	Canada	[302]
		KIR2DS3	+	Yes	366	PA	Canada	[302]
	19q13.41	ZNF816	rs9304742	Yes	$\underline{9135}_5$	P	China, Ger	**G [458]**
				No	596	P	US	**G [458]**
			rs11084211	Yes	2470	P	US	**G [458]**
20	20p13	ADAM33*	rs597980	Yes	$\underline{2047}_2$	P	US	[283]
				Yes	126_f	P	France	[278]
			rs512625	No	1448	P	US	[283]
				Yes	150	P	France	[434]
				Yes	126_f	P	France	[278]
			rs677044	No	1448	P	US	[283]
				No	150	P	France	[434]
				Yes	126_f	P	France	[278]
			rs44707	No	1448	P	US	[283]

				Yes	126_f	P	France	[278]
			rs628977	No	150	P	France	[434]
				>Yes	74	P1	France	[434]
				No	126_f	P	France	[278]
		SIGLEC1	rs6076542	Yes	126_f	P	France	[278]
	20q12	SDC4	rs1008953	Yes	$\underline{5895}_2$	P	Eur, US, Can	**G [455]**
	20q13.13	SLC9A8	rs6020100, rs645544	Yes	1747	P1	UK	**G [64]**
		RNF114	rs2235617	Yes	2622	P	UK, Ireland	**G [453]**
				Yes	1747	P1	UK	**G [64]**
			rs1056198, rs6125829, rs2235616, rs636987	Yes	1747	P1	UK	**G [64]**
	20q13.1-q13.2	SPATA2	rs495337	Yes	$\underline{5895}_2$	P	Eur, US, Can	**G [455]**
				No	1448	P	US	[283]
				Yes	$\underline{2679}_2$	P1	UK, Germany	**G [64]**
			rs2769982	Yes	1747	P1	UK	**G [64]**
21	21q22	Intergenic	rs2836754	Yes	1256	P1	UK	[530]
	21q22.2	FLJ45139	rs2836754	No	1448	P	US	[283]
				Yes	1256	P1	UK	[530]
22	22q11.23	GSTT1	null allele	Yes	327	P	Germany	[396]
				No	100	P1	Germany	[395]
		MIF	-173G/C	No	207	P1	China	[536]
				Yes	33	P2	China	[536]
				Yes	228	P	UK	[112]
			-794CATT	No	240	P	China	[536]
				Yes	228	P	UK	[112]

Chr, chromosome; Locus, as published by the *NCBI*; Gene, given by its 'Official Gene Symbol' (aliases, gene name and location provided in the List of Genes); Variant, given by its base number (*GenBank*) or SNP ID (*NCBI SNP database*); Ass, states if an association was found or not; Size, sample size given by the number of cases (or families $_f$); Clinic, clinical psoriasis variant/s; P, psoriasis without further specification; P1, early-onset psoriasis (Type 1); P2, late-onset psoriasis (Type 2); PA, psoriatic arthritis; PG, guttate psoriasis; PPP, palmoplantar pustulosis; PPA, psoriasis without further specification and psoriatic arthritis; sp, sporadic; fa, familiar; med, allergic reactions to medication; Country, where the study populations reside; Ref, reference; *, these genes show both positive and negative reports for deviating variants; $_f$, family study; $\underline{100}_{2/3/4}$, sample consisting of 2,3 or 4 subsamples; G, this reference is a genome-wide association study.

B.2. Negative reports for psoriasis

Table B.2.: Genetic variants without evidence of association with psoriasis

Chr	Locus	Gene	Variant	Ref
1	1p36.3-p36.2	MASP2	D105G	[452]
		TNFRSF1B	+676T/G	[391]
			+1663, +1668, +1690	[3]
	1p31.3-p31.2	IL12RB2	rs1109918	[69]
	1p31.3	IL23R*	rs1004819, rs10489629, rs1343151	[65, 117, 384]
			rs7517847	[65, 384]
			rs10889677, rs11209032	[117, 384]
			rs11465804	[117]
			rs11465817, rs1343152	[538]
			rs1495965	[384]
			rs1884444	[69]
	1p13.3-p13.1	PTPN22*	rs2542151	[530]
	1q21	LOR	rs943967	[457]
			85A/G, -1544G/A, 64_69dup, 567_578del, 684A/G, 716A/T	[148]
		PGLYRP3*	rs821431	[226, 457]
			rs2771110, rs843971, -354	[457]
			rs821427, rs821426, rs821419	[226]
		PGLYRP4*	rs821432, rs2288990, rs3014864	[226]
			rs12096209	[457]
		S100A2	185A/G	[451]
		S100A7	-559G/A, -563A/G	[426]
			rs3006412, rs3006414, rs3014818	[226]
		S100A8	rs11205280, rs3006488, rs4845346	[226]
		S100A9	rs3014866	[226]
			rs2916193	[457]
	1q21.3	FLG*	R501X, 2282del4	[74, 560, 205]
			rs1933064	[360]
	1q21-q22	SPRR1A	rs2879490, rs1999886, rs1415967	[226]
		SPRR1B	rs4240868, rs2339491, rs3806222, rs1933382, rs423692	[226]
		SPRR2B	rs581447, rs440598	[226]
		SPRR2E	rs3843257, rs405618	[226]
		SPRR2C	rs2928	[226]
	1q24	Intergenic	rs12037606	[283]
	1q31-q32	IL10*	-592C	[28, 533, 77, 24]
			-819C/T	[28, 244, 77]
			-3575A/T	[533]
	1q32	IL20*	1462A/G	[248, 246]
		IL24	rs3762344, rs1150253, rs1150256, rs1150258	[248, 251]
			rs291111	[251]
	1q32.2	IL19*	rs2243158, rs2243168, rs2073186, rs2243174, rs2243191, rs2243193	[248, 250]
2	2p25	ACP1	A, B, C	[307]
	2p21	CYP1B1	*1, *3	[396]
	2q12	IL1R1	970C/T	[388]
	2q12-q14.1	IL1F6	rs895497, rs2289934	[387]
		IL1F7	rs2723187	[387]
		IL1F8	rs1562304, rs1900287	[387]
	2q12-q21	IL1F9	rs2121335	[387]
	2q13	IL1F10	rs3811058	[387]
	2q14	IL1A*	rs2856836, rs3783550, rs3783547, rs3783543, rs17561, rs1533463, rs2071373, rs3783572, rs3783526, rs1800794	[387]
		IL1B*	+3953C/T	[387, 370, 388, 24, 392]
			rs1143643, rs1143637, rs3917360, rs1143630, rs3917354, rs3917348	[387]
		IL1F5	rs990524	[387]
	2q33	CTLA4	-18C/T, -1147C/T	[290, 485]

			+49A/G	[133, 291, 290, 245, 485]
			(AT)n	[4]
			CT60A/G	[291]
	2q37.1	ATG16L1	rs10210302	[530]
	3p25	PPARG	rs1805192, rs1800571, rs3856806	[54]
3	3p21.31	CCR5	- 32bp del, rs1799988	[445]
	3q21	CSTA	1, 3	[417]
		ZNF148	1, 2, 3	[417]
		Intergenic	rs1554241, rs702045	[4]
	3q25.33-q26	IL12A	rs583911, rs2227314, rs2243131, rs2243149, rs2243154, rs6771983, rs2371494, rs11171806, rs2914119	[69]
4	4q13-q21	IL8	rs4073	[77]
	4q21-q25	SPP1	616G/T, 443T/C, 302A/C, 156ins, 1083A/G, 1239C/A	[88]
	4q26-q27	FGF2	rs1048201	[55]
	4q28.3	MGST2	g.-1227C/T, g.-49A/G, g.5492GT/C, g.29288T/C, g.34644C/G, g.39951A/G	[543]
	4q31	IL15*	rs10519613	[283, 436, 516]
			rs1057972	[283, 436]
			rs2254514, rs3806798, rs35221404, rs2322303, rs10519612, rs1040257, rs12510514, rs932209, rs17461269, rs1519551, rs990851, rs12508866	[436]
	4q34.1-q34.3	VEGFC	rs4146612, rs3775194, rs2046463	[273]
	4q34.1-q35.1	IRF2	921G/A	[136]
5	5q31	FGF1	rs34011	[55]
		SLC22A4/5*	rs1050152, rs3792876	[183, 141]
			rs3763112, rs1007602, rs2073838, rs272887, rs2304081, rs2306772, rs2269822	[183]
	5q31.1	CD14	-159C/T	[232]
		IL4*	+33C	[77]
	5q31.1-q33.1	IL12B*	rs2569254, rs10631390, rs1787508, rs17875322	[77]
	5q31-q32	ADRB2*	Gln27Glu	[362]
	5q34	miRNA-146a	rs2010164	[84]
	5q35.3	FLT4*	- 454T/C, IVS1+2240G/A, IVS1+3064G/A, IVS1-2026G/C, IVS1-185T/C, IVS8+694T/C, IVS8-759G/A, Y448Y, IVS10+761G/A, IVS10+882G/A, IVS13-64G/C, IVS16-104G/A, P1066P, IVS23-820C/A, IVS29-220G/A, 6293T/C, 7811T/C, 10435G/A, 11901T/G, 12506G/C	[273]
6	6p12	IL17F	7488T/C	[431]
		VEGFA*	-2578A/C	[534]
				[55]
			-116G/A, -160C/T	[29]
			-1154G/A	[55]
				[512]
			rs9381249, rs2146323, rs2025033, rs3025035, rs10434	[273]
			rs833061, rs25648	[512]
	6p21.3	AGER*	1704G/T, 2245A/G	[499]
		C4A*	1, 2	[325]
		C4B*	5, R	[325]
		C6orf15	247, 492, 493, 558, 900	[418]
		CCHCR1*	477	[19]
			386, 404, 904, 1328, 1364, 1471, 2406, 384, 556, 571, 614, 850, 1178, 1329, 1354, 1426, 1579, 1601, 1802, 1959, 1990, 2254, 2257, 2277, 2278	[349]
			249, 436, 715, 769, 1193, 1194, 1219, 1229, 1667, 1824, 1855, 1861, 2122, 2271	[17]
		CDSN*	+1240G/T	[76, 304, 82, 152, 213]
			1331	[76, 402, 358]
			9, 614, 1606	[76, 402]
			767, 1118, 1593	[76, 358]
			63, 137, 180, 206, 442, 420, 1372, 1675, 1740, 1748, 1907, 1938	[76]

		Intergenic	rs2284177, rs3094207, rs3094205, rs3095307, rs3094198, rs3130558, rs3130560, rs3823418, rs2074478	[434]
		LTA*	+10A, +80A, +252G, +368C, +495C, +723C	[77]
		PSORS1C1*	Poly C 6 386-392, Poly C 3-4 748-751	[80]
			39686C/T, 26710G/T, 26670C/T, 25521 G/A	[194]
		PSORS1C2*	26079G/A, 27104G/A, 27278C/T	[194]
			32 G/A, 64 G/A, 68 C/T, 88 A/G, 226 T/C, 389 G/A, 466 G/A, 563 C/T, 565 C/T, 782 C/T, 821 A/G, 1041 C/T	[83]
		TAP1*	333	[379, 500, 191]
		TAP2*	379, 565	[379]
		TCF19	2712 G/A, 2738C/A/G, 2803 C/T, 4bp deletion 3340-3343 (CTTC)	[476]
		TNF*	-1031C	[77, 391, 385, 165, 334]
			-863A	[77, 385, 165, 334]
			+488G/A	[3]
			-307G/A, -237G/A	[334]
	6p21.31	POU5F1*	A	[303]
			-254C, -19A, 83T, 119A, 821G, 1103C, 1262del	[78]
			+103T, +1140T	[82]
			allele 2	[357]
	6p21.33	MICA*	002, 004, 008, 009, 010, 012, 016, 017, 018, 019, 026, 052	[403]
		PSORS1C3*	rs3130506, rs3868542, rs2269711	[76, 195]
			rs15721494	[195]
			434G/A, 441G/C	[76]
	6p24.1	EDN1	G(8002)A	[501]
			- 134 3A/4A	[515]
		GFRA4	rs692862, rs633924, rs2853208, rs6084432	[278]
	6p22.2-p21.3	PRL	- 1149G/T	[450]
	6q22.33-q23.1	IL20RA*	rs4896227, rs276586, rs276526, rs276571, rs719640, rs276466, rs7749054, rs1343677, rs2797665,rs12197182	[249]
	6q25	SUMO4	rs237025A/G	[280]
7	7q31.3	LEP	-2548G/A	[229]
	7q32	IRF5	rs2004640, rs2070197, rs10954213, rs2280714	[419]
X	Xp22.31	FIGF	-330G/A rs6632528, IVS5-698C/A rs6527518	[273]
	Xp11.23	FOXP3*	-6054deletion/ATT, -924A/G	[144]
	Xq28	IRAK1*	rs1059703	[84]
8	8p22	NAT2*	481C/T, 590G/A, 282C/T, 341T/C 803A/G	[254]
			rapid acetylators 4	[395]
9	9q34.3	RXRA*	-25A/G	[497]
10	10q24.1-q24.3	CYP2C19	1A, 2A	[396]
	10q24.3-qter	CYP2E1	1A, 5B	[396]
11	11q13	RELA	rs2009453, rs6591183	[58]
12	12p13.2	TNFRSF1A	+36A/G	[391]
	12q13.11	VDR*	FokI	[108, 164, 408, 237]
			A-1012G	[164]
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