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Genetics of Pancreatitis: A Guide for Clinicians

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Chronic pancreatitis · Genetics · CTRC · CFTR · PRSS1 · PRSS2 · SPINK1

Abstract
It is now generally believed that pancreatitis results from pancreatic autodigestion. An inappropriate conversion of pancreatic zymogens to active enzymes within the pancreatic parenchyma is thought to initiate the inflammatory process. A key role has been attributed to the activation of trypsinogen to trypsin, converting all proteolytic proenzymes to their active form. Several gain-of-function mutations in the cationic trypsinogen gene *(PRSS1)* have been identified in patients with chronic pancreatitis (CP). These mutations lead to enhanced intrapancreatic trypsinogen activation. In contrast, a variant in the anionic trypsinogen *(PRSS2)* gene, p.G191R, has been described that mitigates intrapancreatic trypsin activity and thereby plays a protective role. Beside trypsinogen mutations, loss-of-function variants in *SPINK1*, encoding a pancreatic trypsin inhibitor, are strongly associated with idiopathic CP. Approximately 15–40% of patients with so-called idiopathic CP carry p.N34S on one allele or on both alleles. Chymotrypsin C (CTRC) degrades all human trypsin isoforms with high specificity. Two *CTRC* alterations, p.R254W and p.K247_R254del, are significantly associated with idiopathic as well as alcohol-related CP. Functional analysis of the variants revealed impaired activity and/or reduced secretion. Thus, loss-of-function mutations in *CTRC* predispose to pancreatitis by diminishing its protective trypsin-degrading activity. Albeit the association between *CFTR*, the gene mutated in cystic fibrosis, and idiopathic CP is now well established, the pathogenic mechanisms are poorly understood. Nearly 25–30% of patients carry at least one *CFTR* mutation, but few patients only were compound-heterozygous. Several patients, however, are trans-heterozygous for a *CFTR* alteration and a *PRSS1, SPINK1,* or CTRC variant, respectively.
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Introduction

Chronic pancreatitis (CP) is characterized by progressive and irreversible damage to both exocrine and endocrine components of the pancreas, eventually resulting in significant insufficiency of the organ with maldigestion and diabetes mellitus. The incidence of CP reported in industrialized countries has been estimated to approximately 3.5–10 per 100,000 inhabitants. Chronic alcohol abuse is the major cause of CP in Western countries, but other factors such as genetic alterations, obstruction of the pancreatic duct due to strictures, hypercalcemia, hypertriglyceridemia, and autoimmunity have also been implicated. Prominent morphological features of early-stage disease are necrosis, interlobular fibrosis and pseudocysts, whereas in late-stage CP acinar destruction, severe intralobular fibrosis, variable pancreatic duct lesions and ductal stones are characteristic findings.

Nearly 60 years ago, it was recognized for the first time that CP clusters in selected families suggesting an inherited basis in these patients [1]. The underlying genetic de-

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fect remained obscure for more than 40 years. As stated in this first report on inherited pancreatitis, 'hereditary chronic relapsing pancreatitis does not present earmarks which distinguish it from non-hereditary chronic relapsing pancreatitis' [1]. In 10–30% of patients suffering from CP, no apparent underlying cause, including heredity, can be identified. Recent research indicates that a significant percentage of these patients with so-called 'idiopathic CP' also have a genetic basis for their disorder. This review delineates the different genes involved in the pathogenesis of hereditary or idiopathic pancreatitis, the impact of these genetic discoveries on other types of CP such as alcohol-related CP, and the implications for disease pathogenesis.

Cationic Trypsinogen *(PRSS1)*

In 1896, Hans Chiari [2] postulated that pancreatitis results from pancreatic autodigestion. An inappropriate conversion of pancreatic zymogens to active enzymes within the pancreatic parenchyma was proposed to initiate the inflammatory process. A key role has been attributed to the activation of trypsinogen to trypsin, converting all proteolytic proenzymes to their active form. In human pancreatic juice, three different trypsinogens have been described and designated, according to their electrophoretic mobility, as cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2) and mesotrypsinogen (PRSS3). Compared to the anionic isoenzyme, the cationic trypsinogen autoactivates more easily and is more resistant to autolysis.

By linkage analysis, several groups located a gene for hereditary pancreatitis on the long arm of chromosome 7 (7q35). Subsequently, a mutation in the cationic trypsinogen gene, also referred to as serine protease 1 *(PRSS1)* (OMIM 276000), has been identified as underlying defect. In five families, a c.365G>A transition leading to a substitution of arginine by histidine at codon 122 (p.R122H) segregated with the disease [3]. So far, p.R122H appears to be the most common *PRSS1* mutation worldwide.

Various other *PRSS1* alterations have been reported in subsequent studies. These variants have been found in families with suspected hereditary pancreatitis as well as in patients without a family history. With the exception of p.A16V, p.N29I, p.N29T, p.R116C, and p.R122C, however, these variations have been reported in single patients or families only, and a detailed clinical background was mostly not given. Thus, their pathogenic significance remains largely to be elucidated (for detailed information of the different variants see: www.uni-leipzig.de/pancreasmutation).

Although the precise disease mechanisms have not been unraveled, it is now a generally accepted model that an increased intrapancreatic trypsin activity results in pancreatitis. Site-directed mutagenesis of recombinant human cationic trypsinogen revealed that almost all of the mutations studied (e.g. p.N29I and p.R122H) enhance significantly autoactivation in vitro, whereas some mutations such as p.R122H additionally inhibit autolysis of the active enzyme [4]. Thus, gain-of-function mutations leading to enhanced intrapancreatic trypsinogen activation may be the common initiating step of pancreatitis caused by *PRSS1* mutations, whereas stabilization of trypsin may be an accessory mechanism.

So far, only two *PRSS1* variants, p.A16V and p.E79K, display unique features: recombinant p.E79K trypsinogen showed in vitro unaltered catalytic activity, autolysis, and trypsin inhibitor inhibition. Instead, p.E79K activated anionic trypsinogen, PRSS2, at least twofold better than wild-type cationic trypsin. Thus, p.E79K leads to increased trypsinogen activation by trans-activation of PRSS2 instead of autoactivation [5]. However, since p.E79K was found in a similar frequency in control subjects, its pathogenic relevance remains to be elucidated.

Hereditary pancreatitis was initially defined as an autosomal dominant disease with a penetrance of 70–80% [1]. The clinical characteristics of most families with p.R122H or p.N29I are in line with this concept. In contrast, the third most common *PRSS1* variant p.A16V was almost exclusively found in patients without a family history of pancreatitis, indicating that *PRSS1* mutations do not show exclusively a dominant inheritance pattern [6]. Thus, trypsinogen mutations display a considerable variability of penetrance. Initially, enhanced autoactivation was proposed as a pathogenic mechanism, however, studies on recombinant p.A16V failed to demonstrate this effect. Instead, p.A16V PRSS1 showed a fourfold increased rate of activation peptide processing mediated by chymotrypsin C (CTRC) resulting in accelerated trypsinogen activation in vitro [7].

Recently, a triplication of an approximately 605-kb segment containing *PRSS1* and *PRSS2* was reported in five families with hereditary pancreatitis. Thus, beside point mutations, a gain of trypsin through a gene dosage effect may also contribute to the disease pathogenesis [8].

The importance of *PRSS1* mutations as pathogenic mediators in hereditary pancreatitis is also underscored by a transgenic mouse model expressing mutant R122H mouse trypsinogen. Pancreata of the transgenic mice dis-

played early-onset acinar injury, inflammatory cell infiltration, and enhanced response to cerulein-induced pancreatitis. With progressing age, pancreatic fibrosis and acinar cell dedifferentiation developed [9].

Anionic Trypsinogen *(PRSS2)*

Because increased proteolytic activity due to mutated *PRSS1* enhances the risk for CP, we postulated that mutations in the anionic isoenzyme *PRSS2* (OMIM 601564) might also act disease predisposing. Analyzing *PRSS2* in CP patients and controls, however, revealed a c.571G>A transition resulting in a glycine by arginine exchange at residue 191 (p.G191R), which was over-represented in control subjects. p.G191R was found in 220 out of 6,459 (3.4%) controls but only in 32 out of 2,466 (1.3%) patients (odds ratio (OR) 0.37; $p = 1.1 \times 10^{-8}$). In contrast to unaffected Caucasians, who showed a p.G191R frequency of 3.4%, the variant was rare in individuals of African descent (2/948) with an estimated overall frequency of 0.2% (0,0.5), which was significantly different to the frequency we found in Europeans ($p = 10^{-11}$) [10].

Further analyses showed that patients with p.G191R were of higher age than those without the protective variant. In the idiopathic/hereditary pancreatitis group p.G191R was found in 24/1,256 (1.9%) patients older than 20 years compared to 3/601 (0.5%) patients of younger age ($p = 0.021$). A similar tendency was observed in the alcohol-related CP group: none of the 162 patients with an age of 40 years or younger showed p.G191R compared to 5/447 (1.1%) of patients older than 40 years [10].

Recombinant expression of wild-type and p.G191R PRSS2 showed that both the physiological activator enteropeptidase (enterokinase) and trypsin strongly activate wild-type PRSS2, and the trypsin activity generated remained stable over the entire time period studied. In contrast, the p.G191R variant showed only minimal or no tryptic activity after activation. The proteolytic processing of p.G191R was further characterized by mass spectrometry. After incubation with enteropeptidase, wild-type trypsinogen was converted to trypsin, whereas the p.G191R mutant proenzyme was rapidly converted to cleavage products of molecular masses corresponding to the N-terminal peptide 16-191 and the C-terminal peptide 192-247. Intact p.G191R trypsin was nearly undetectable [10].

Taken together, upon activation by enterokinase or trypsin, purified recombinant p.G191R protein showed a complete loss of trypsin activity due to the introduction of a novel tryptic cleavage site that renders the enzyme hypersensitive to autocatalytic proteolysis. Thus, the p.G191R PRSS2 alteration reduces intrapancreatic trypsin activity and might thereby play a protective role against CP.

Serine Protease Inhibitor, Kazal Type 1 *(SPINK1)*

The serine protease inhibitor, Kazal type 1 *(SPINK1)* (OMIM 167790), also known as pancreatic secretory trypsin inhibitor (PSTI), is a potent anti-protease that is thought to be a major inactivation factor of intrapancreatic trypsin activity. SPINK1 was first isolated in the bovine pancreas by Kazal and co-workers in 1948. SPINK1 possesses a reactive site that serves as a specific target substrate for trypsin. However, trypsin inhibition by SPINK1 is only temporary because the trypsin-SPINK1-complex itself represents as substrate for trypsin, resulting in a subsequent degradation of the inhibitor molecule and in restoration of the original trypsin activity [11].

A considerable number of patients with hereditary pancreatitis do not show a *PRSS1* mutation, suggesting that genetic defects in other genes might be involved in the disease pathogenesis. Since gain-of-function mutations in *PRSS1* leading to a 'super trypsin' cause pancreatitis, we hypothesized that pancreatitis may also be caused by loss-of-function mutations in pancreatic trypsin inhibitors. In 2000, we identified *SPINK1* as another pancreatitis gene: in 18 out of 96 unrelated pediatric patients, a c.101A>G transition leading to substitution of asparagine by serine at residue 34 (p.N34S) was found; 6 patients were homozygous for this mutation [12]. No phenotypic differences between heterozygous and homozygous p.N34S patients were detected. The association between p.N34S and CP has been confirmed by numerous others. p.N34S is mostly found in patients without a family history of CP: 15–40% of patients with so-called idiopathic CP carry p.N34S on one allele or on both alleles. Data taken from eight larger studies in Europe and the USA indicate that 12.6% of patients with CP were heterozygous for p.N34S, and 3.6% were homozygous. In contrast, homozygous individuals were never identified among these controls, whereas heterozygosity was detected at 1.9% on average. In summary, *SPINK1* mutations represent so far the strongest genetic risk factor in so-called idiopathic CP. The importance of mutated *SPINK1* is furthermore underlined by the finding of p.N34S in about half the patients with tropical calcific pancreatitis from India [13, 14].

The pathogenic action of p.N34S, however, remains elusive. Recombinant p.N34S mutated human SPINK1 did not show any altered trypsin inhibitor capacity [15, 16].

The second most common *SPINK1* mutation, c.194 + 2T>C, affects in third intron the position 2 of the splice donor site, which is highly conserved in eukaryotes. Analysis of mutated mRNA showed a truncated *SPINK1* due to skipping of exon 3 [17].

Several other *SPINK1* alterations have been described during the recent years, mainly in single patients or families only (for detailed information of the different variants see: www.uni-leipzig.de/pancreasmutation). With the exception of few mutations which highly suggest a loss of function by destruction of the ATG initiation codon (p.M1?) or by shift of reading frame with premature termination (c.27delC, c.98dupA), the functional consequences of most variants are unknown. Recently, expression studies of two dominant inherited mutations affecting the signal peptide, c.41T>C (p.L14P) and c.41T>G (p.L14R), reported a rapid intracellular degradation of the mutant inhibitor molecules leading to abolished SPINK1 secretion [18]. More pronounced as in *PRSS1*, *SPINK1* mutations display a marked variability of penetrance and inheritance pattern. Some variants that most probably lead to complete functional loss of the mutated allele, such as M1?, c.27delC, or the codon 14 mutations, appear to follow a dominant trait, whereas the N34S alteration may decrease the SPINK1 capacity less, resulting in recessive or complex trait.

So far, two genetically engineered animal models evaluated the role of SPINK1 in pancreatitis. Transgenic expression of rat *Spink1* in mice, which leads to an increased endogenous trypsin inhibitor capacity by 190%, reduced significantly the severity of cerulein-induced pancreatitis [19]. Targeted disruption of *Spink3*, the murine homologue of human *SPINK1*, resulted in autophagic degeneration of acinar cells, impaired regeneration, and death within 2 weeks after birth [20]. Neither significant inflammatory cell infiltration nor enhanced acinar trypsin activity were observed. By using a more sensitive assay, however, enhanced tryptic activity in pancreatic acini of *Spink3*–/– mice prepared 1 day after birth was detected [21].

Chymotrypsinogen C *(CTRC)*

CTRC (OMIM 601405), also known as caldecrin, was first isolated from porcine pancreas in 1992. Recently, striking evidence that CTRC may be identical with the so-called enzyme Y, an obscure trypsinogen-degrading activity in the human pancreatic juice, has been reported [22]. CTRC is capable of degrading all human trypsin isoforms with high specificity [22]. No other pancreatic protease tested (such as chymotrypsin B1 or B2 and elastase 2A, 3A or 3B) displayed trypsin or trypsinogen-degrading activity. Thus, *CTRC* emerged as a strong novel candidate for a pancreatitis-associated gene.

Indeed, a recent study reported an increased frequency of *CTRC* variants in patients with CP compared to control subjects [23]. Analyzing German subjects with idiopathic or hereditary CP by DNA sequencing of all 8 exons of the 8.2-kb-long *CTRC*, several *CTRC* variants were detected, the large majority of which in exons 2, 3, and 7. Altogether, 11 missense and 2 deletion variants in *CTRC* were identified. The two most frequent variants, c.760C>T (p.R254W) and c.738_761del24 (p.K247_R254del), both located in exon 7, were found in affected individuals with a frequency of 2.1 and 1.2%, respectively. Taken together, the two alterations were significantly over-represented in the pancreatitis group (30 out of 901; 3.3%) compared to controls (21 out of 2,804; 0.7%) (OR = 4.6; CI = 2.6–8.0; $p = 1.3 \times 10^{-7}$) [23]. The variant c.738_761del24, which causes an in-frame deletion of 8 amino acids from Lys247 through Arg254 (p.K247_R254del), showed the strongest disease association (OR = 11.5; CI = 3.2–41.5; p = 0.00003). Subgroup analysis for these two heterozygous variants revealed a similar frequency in the hereditary 6/143 (4.2%; 6× p.R254W) and idiopathic 24/758 (3.2%; 13× p.R254W; 11× p.K247_R254del) groups. To confirm these findings in an independent cohort with another inflammatory pancreatic disease, a replication study on subjects with alcohol-related pancreatitis was performed. Again, the two CTRC variants, p.R254W and p.K247_R254del, were found in 10/348 (2.9%) individuals with CP but only in 3/432 (0.7%) subjects with alcoholic liver disease without CP (OR = 4.2; CI = 1.2–15.5; p = 0.02) [23]. The association between *CTRC* variants and CP was recently confirmed by a French group [24].

To elucidate the relationship between *CTRC* alterations and *PRSS1* and *SPINK1* variants, all German subjects with idiopathic or hereditary pancreatitis were investigated for p.A16V, p.N29I and p.R122H in *PRSS1* and for p.N34S in *SPINK1*. In total, 52/901 (5.8%) individuals carried a heterozygous *PRSS1* variant, whereas 138/901 (15.3%) were positive for p.N34S (121 heterozygotes, 17 homozygotes). One subject with idiopathic disease was trans-heterozygous for the *PRSS1* p.R122H variant (inherited from the mother) and the *CTRC* p.G217S variant (inherited from the father). None of the 17 *SPINK1* p.N34S homozygotes carried a *CTRC* variant. On the other hand, 9/121 (7.4%) p.N34S heterozygotes were also heterozygous for one of

two pancreatitis-associated *CTRC* variants. In contrast, only 21/763 (2.8%) of the patients without p.N34S were heterozygous for p.R254W or p.K247_R254del (p = 0.014; p.N34S heterozygous vs. p.N34S wild type). 16 out of 902 (1.8%) control subjects were p.N34S heterozygous, but none of the 16 carried a *CTRC* variant. In the Indian population, 3 controls (3.6%) were heterozygous for p.N34S but did not carry any *CTRC* alteration. Among the patients with tropical pancreatitis, 29/71 (40.9%) were positive for p.N34S. Remarkably, none of the 7 homozygotes, but 6/22 (27.3%) of the heterozygotes carried a *CTRC* variant (1 individual was compound-heterozygous for p.A73T and p.D260N). In contrast, only 3/42 (7.1%) individuals with wild-type *SPINK1* were heterozygous for a *CTRC* variant (p = 0.051; p.N34S heterozygous vs. p.N34S wild type) [23].

As observed previously for other pancreatitis-associated gene alterations, the majority of the identified *CTRC* variants do not alter the reading frame of the translated CTRC protein. The two exceptions are the c.190_193delATTG (p.I64LfsX69) and the c.308delG (p.G103VfsX31) variants, which cause a shift in the reading frame and may result in a truncated polypeptide chain. Alternatively, the mRNA of these mutants may undergo nonsense-mediated decay and thus result in no CTRC protein whatsoever. In any event, these frameshift variants are expected to cause a complete loss of CTRC function. To investigate the functional consequences of the *CTRC* alterations, wild-type and mutant CTRC were expressed in human embryonic kidney (HEK) 293T cells via transient transfection. Secretion of p.K247_R254del was severely diminished relative to the wild type. In contrast, CTRC activity secreted by cells expressing the p.R254W mutant was reduced to about 50% of wild type. SDS-PAGE of conditioned media revealed that secreted levels of p.R254W were about 40% of wild-type CTRC, suggesting that the functional defect in this mutant is decreased secretion rather than impaired catalytic activity [23].

In summary, the functional analyses of the CTRC variants revealed impaired activity and/or reduced secretion indicating that loss-of-function alterations in *CTRC* predispose to pancreatitis by diminishing its protective trypsin-degrading activity.

Cystic Fibrosis Transmembrane Conductance Regulator *(CFTR)*

Cystic fibrosis (CF) represents an autosomal recessive inherited disorder characterized by chronic obstructive pulmonary disease with proximal bronchiectasis often resulting in chronic lung failure, by exocrine pancreatic insufficiency with maldigestion, and by elevated sweat chloride concentrations. Other clinical features include liver fibrosis, meconium ileus, and male infertility due to obstructive azoospermia. In 1989, *CFTR* (OMIM 602421) was identified as the CF gene by linkage analysis and positional cloning [25]. *CFTR* belongs to the ATP-binding cassette (ABC) superfamily and encodes a transmembrane protein present at the surface of most epithelial cells functioning as a cyclic adenosine monophosphate (cAMP)-responsive chloride channel.

In 1998, two studies described an association between CP and *CFTR* variants [26, 27]. The link between CF and CP is supported by the findings that both conditions may show abnormal sweat chloride contents as well as pancreatic ductal obstruction due to inspissated secretions. Moreover, some patients with CF suffer from recurrent attacks of pancreatitis.

One study tested 134 patients with CP, including 60 cases with idiopathic and 71 cases with alcohol-induced disease, for 22 mutations [26]. 18 patients (13.4%), including 12 with idiopathic CP (20%), were heterozygous for a *CFTR* mutation. The frequency of *CFTR* mutations in alcohol-related CP was twice and in idiopathic CP four times as expected. In the other study, 17 *CFTR* mutations in 27 patients with idiopathic CP were investigated [27]. 7 patients (25.9%) had at least one *CFTR* mutation and 1 patient was compound-heterozygous. The frequency of *CFTR* mutations in idiopathic CP was six times higher than expected.

CFTR mutations can be divided into five or six general classes which reflect their known or predicted molecular dysfunction [28]. Class I–III mutations generally affect the amount of functional CFTR more seriously than class IV and V mutations, and are usually associated with a classic CF.

Albeit the association between *CFTR* and idiopathic CP is now well established, the pathogenic mechanisms are poorly understood. One may speculate that idiopathic CP represents nothing else than 'atypical' CF caused by the combination of two mild or of one mild and a severe *CFTR* mutation. Subsequent studies analyzing the complete *CFTR* coding sequence as well as *PRSS1* and *SPINK1* found that 25–30% carried at least one *CFTR* mutation, but few patients only were compound-heterozygous [29, 30]. Several CP patients, however, were trans-heterozygous for a *CFTR* alteration and a *SPINK1, CTRC,* or *PRSS1* variant, respectively, illuminating the significance of the combination of mutations in different genes in the disease pathogenesis [23, 29, 30].

These data are in line with our own observations, in which only few patients with CP were compound-heterozygous for CFTR mutations, but a considerable number of individuals were trans-heterozygous for *CFTR* and *PRSS1*, *SPINK1* and *CTRC* variants [Rosendahl et al., unpubl. data]. Moreover, patients with CP were predominately heterozygous for 'mild' *CFTR* variants, i.e. class IV variants such as p.R117H, indicating that a specific loss of a *CFTR* sub-function such as disturbed bicarbonate secretion might be the underlying pathological mechanism in *CFTR*-related pancreatitis.

Alcohol-Related Chronic Pancreatitis

The association between alcohol abuse and pancreatitis is well established, but individual susceptibility to alcohol varies widely and only 5–10% of heavy drinkers develop CP [31]. Increasing evidence portends that additional environmental or genetic cofactors are necessary, which are mostly unknown. Several studies investigating *PRSS1*, pancreatitis-associated protein *(PAP)*, α_1-antitrypsin *(PI)*, *CFTR*, cytokeratin 8 *(KRT8)*, MHC antigens, and alcohol-metabolizing or -detoxifying enzymes gave negative or conflicting results.

Since xenobiotic-mediated cellular injury is thought to play a major role in the pathogenesis of alcoholic CP, genetic variations reducing the activity of detoxifying biotransformation enzymes might be of particular importance. Recently, a low detoxification activity allele of the UDP-glucuronosyltransferase 1A7, *UGT1A7*3*, has been linked to pancreatic cancer and alcoholic CP [32]. Subsequent studies, however, could not confirm these data and showed that the previously reported association was based on primer-dependent genotyping errors [33].

In a large multicenter study, an association between mutated *SPINK1* and alcoholic CP has been described: 16/274 (5.8%) patients with alcoholic CP, but only 4/540 (0.8%) healthy control individuals and 1/98 (1.0%) alcoholic controls without CP carried p.N34S [34]. Subsequent studies observed a p.N34S frequency in alcohol-related CP of 5.6, 6.0, and 6.3%, respectively. Recently, a protective *PRSS2* variant, p.G191R, has been described that was significantly less common in patients with alcoholic CP compared to controls (5/609 (0.8%) vs. 220/6,459 (3.4%); $p < 0.0001$) [10].

Interestingly, analysis of pancreatic juice showed an elevated trypsinogen/trypsin inhibitor ratio in alcoholics compared to non-alcoholic controls, indicating a weakening of the defense mechanism provided by the trypsin inhibitor against premature zymogen activation [35].

Beside the *SPINK1* p.N34S variant, genetic alterations of *CTRC* have also been associated with alcoholic pancreatitis (see above) [23].

Conclusion

The genetic studies about inherited pancreatitis have substantially changed our disease understanding. For a long time, hereditary pancreatitis was thought to be a rare disorder. The recent findings of *PRSS1*, *SPINK1, CTRC* and *CFTR* mutations in patients with so-called idiopathic CP, however, demonstrate that inherited cases of CP are much more common than originally envisioned. These data challenge the differentiation between 'hereditary' and 'idiopathic' pancreatitis. Different mutations in different genes might lead to different phenotypic presentations and inheritance pattern and even the same mutation in the same gene might have different consequences depending on the individual's genetic background and environmental factors. The discovery of *SPINK1* and *CTRC* mutations in other types of CP such as tropical calcific pancreatitis [13, 14, 23] and alcohol-induced CP [34] further blur the borders between the particular CP subtypes. Thus, the identification of further genes involved into the pathogenesis of inherited CP probably will also enhance our knowledge about more common types of CP such as alcoholic or tropical CP. Future research will most likely reveal a very complex interaction between various environmental and genetic factors with flowing transitions among these subtypes.

Disclosure Statement

The author has no conflict of interest to declare.

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