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SHORT REPORT

A multi-centre clinico-genetic analysis of the VPS35 gene in Parkinson disease indicates reduced penetrance for disease-associated variants

Manu Sharma,^{1CA} John P A Ioannidis,² Jan O Aasly,³ Grazia Annesi,⁴ Alexis Brice,^{5,6,7} Lars Bertram,⁸ Maria Bozi,^{9,10,11} Maria Barcikowska,¹² David Crosiers,^{13,14,15} Carl E Clarke,¹⁶ Maurizio F Facheris,¹⁷ Matthew Farrer,¹⁸ Gaetan Garraux,¹⁹ Suzana Gispert,²⁰ Georg Auburger,¹⁹ Carles Vilariño-Güell,¹⁸ Georgios M Hadjigeorgiou,²¹ Andrew A Hicks,¹⁷ Nobutaka Hattori,²² Beom S Jeon,²³ Zygmunt Jamrozik,²⁴ Anna Krygowska-Wajs,²⁵ Suzanne Lesage,^{5,6,7} Christina M Lill,^{9,26} Juei-Jueng Lin,²⁷ Timothy Lynch,²⁸ Peter Lichtner,²⁹ Anthony E Lang,³⁰ Cecile Libioulle,¹⁸ Miho Murata,³¹ Vincent Mok,³² Barbara Jasinska-Myga,³³ George D Mellick,³⁴ Karen E Morrison,^{17,35} Thomas Meitner,^{36,37} Alexander Zimprich,³⁸ Grzegorz Opala,³⁶ Peter P Pramstaller,¹⁹ Irene Pichler,¹⁹ Sung Sup Park,²⁶ Aldo Quattrone,⁴ Ekaterina Rogaeva,³⁹ Owen A. Ross,⁴⁰ Leonidas Stefanis,^{11,41} Joanne D Stockton,³⁵ Wataru Satake,⁴² Peter A Silburn,⁴³ Tim M Strom,^{37,39} Jessie Theuns,^{14,15} Eng- King Tan,⁴⁴ Tatsushi Toda,⁴² Hiroyuki Tomiyama,²² Ryan J Uitti,⁴⁵ Christine Van Broeckhoven,^{14,15} Karin Wirdefeldt,⁴⁶ Zbigniew Wszolek,⁴⁵ Georgia Xiromerisiou,²¹ Harumi S Yomono,⁴⁷ Kuo-Chu Yueh,²⁷ Yi Zhao, Thomas Gasser,¹ Demetrius Maraganore,⁴⁸ Rejko Krüger,¹ on behalf of GEOPD consortium

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For numbered affiliations see end of article

Correspondence to

Dr Manu Sharma, Department of Neurodegenerative diseases, Hertie-Institute for Clinical Brain Research and DZNE- German Center for Neurodegenerative Diseases, Tübingen, Hoppe-Seyler-Str. 3, Tübingen 72076, Germany; manu.sharma@uni-tuebingen.de

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ABSTRACT

Background Two recent studies identified a mutation (p.Asp620Asn) in the vacuolar protein sorting 35 gene as a cause for an autosomal dominant form of Parkinson disease. Although additional missense variants were described, their pathogenic role yet remains inconclusive.

Methods and results We performed the largest multi-center study to ascertain the frequency and pathogenicity of the reported vacuolar protein sorting 35 gene variants in more than 15,000 individuals worldwide. p.Asp620Asn was detected in 5 familial and 2 sporadic PD cases and not in healthy controls, p.Leu774Met in 6 cases and 1 control, p.Gly51Ser in 3 cases and 2 controls. Overall analyses did not reveal any significant increased risk for p.Leu774Met and p.Gly51Ser in our cohort.

Conclusions Our study apart from identifying the p.Asp620Asn variant in familial cases also identified it in idiopathic Parkinson disease cases, and thus provides genetic evidence for a role of p.Asp620Asn in Parkinson disease in different populations worldwide.

INTRODUCTION

There is increasing interest to try to identify uncommon and rare genetic variants that increase the risk of common diseases and that are difficult to identify using traditional genome-wide association studies (GWAS) approaches.¹ Rare variants which are not mapped by GWAS can be identified by using next generation sequencing, that is, exome sequencing in large families with multiple affected individuals.² Exome sequencing is now

routinely used to identify rare mutations in familial forms of disease in diverse phenotypes.²

Two recent studies independently performed exome sequencing in large families of Caucasian descent, and identified a mutation in the vacuolar protein sorting 35 (VPS35) gene as a possible cause for an autosomal dominant form of Parkinson disease (PD).^{3,4} In addition, several non-synonymous base exchanges were identified, but their involvement in disease pathogenesis remains inconclusive. Furthermore, recently published studies provided conflicting results regarding the role of VPS35 in PD.⁵⁻⁸ Here, we performed a large multi-centre study to determine the frequency and pathogenicity of VPS35 variants in PD in diverse populations worldwide.

METHODS**Consortium**

Investigators from the Genetic Epidemiology of Parkinson disease Consortium were invited to participate in this study. A total of 23 sites representing 19 countries from four continents agreed to contribute DNA samples and clinical data for a total of 15 383 individuals (8870 cases and 6513 controls). Control individuals underwent neurological examination and were excluded from the study whenever there was clinical evidence for any extrapyramidal disorder.

Genotyping

We selected seven non-synonymous variants exactly as they were proposed.³ In addition, we selected tag single nucleotide polymorphisms

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(SNPs) (HapMap Rel 28 phase II+III, Aug10, National Centre for Biotechnology Information. B36 dbSNP b126; <http://www.hapmap.org>) that cover the common genetic variants in the VPS35 gene using an r^2 threshold of 0.8–1.0 to select tag SNPs for VPS35 gene. Using this strategy, we were able to capture 23 SNPs in a 40 kb region, including VPS35 ('chr16:46 693 589–46 723 144 based on hg 19'). Therefore, in total, 10 SNPs located in the VPS35 were genotyped (including seven rare non-synonymous and three common variants). Genotyping was performed by a central genotyping core. Genotyping was performed using a matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry on a MassArray system (Sequenom, San Diego, California, USA). Cleaned extension products were analysed by a mass spectrometer (Bruker Daltonic, Billerica, MA, USA) and peaks were identified using the MassArray Typer 4.0.2.5 software (Sequenom). Assays were designed by the AssayDesigner software 4.0 (Sequenom) with the default parameters for the iPLEX Gold chemistry and the Human GenoTyping Tools ProxSNP and PreXTEND (Sequenom). All variants were genotyped in one multiplex assay. The average call rate of the variants was >97%. The local Ethics Committee approved the study. All participants gave signed informed consent.

Statistical analysis

Logistic regression was used to test the association between VPS35 and PD in our overall cohort. For common variants (minor allele frequency >5%), we synthesised the effect estimates using fixed and random effects models. Fixed effect models assume that the genetic effect is the same in populations from different sites and that observed differences are due to chance alone. For associations showing between-study heterogeneity, fixed effect estimates yield narrower CIs and smaller *p* values as compared with random effects models, which incorporate between-study heterogeneity.^{9 10} Random effects models allow the genetic effects might be different due to genuine heterogeneity that may exist across different sites. Random effects calculations take into account the estimated between-study heterogeneity. Cochran's Q test of homogeneity and the I^2 metric were used to evaluate the between-site heterogeneity. The I^2 metric ranges from 0% to 100% and measures the proportion of variability that is beyond chance. Typically, estimates of I^2 <25% are considered to reflect little or no heterogeneity, 25%–50% moderate heterogeneity, 50%–75% large heterogeneity and >75% very large heterogeneity. The overall main analysis considered all sites and populations irrespective of ancestry. For variants with minor allele frequency <1%, an exact test was used to compare the frequency differences between cases and controls combining data across all 21 sites.

RESULTS

Characteristics of sites and overall database

Overall, 23 sites contributed a total of 8870 cases and 6513 controls. Characteristics of all participating sites are shown in table 1. Most sites contributed participants of Caucasian ancestry (N=19); four sites included participants of Asian ancestry. The proportion of men and women ranged from 42% to 58% across different participating sites (table 1). The median age at onset of PD in our studied population was 61 years.

Rare variants

Overall, we observed p.Asp620Asn in seven cases, p.Leu774Met in six cases and one control, p.Gly51Ser in three cases and two

controls. Details per site are shown in table 2. The controls subjects carrying p.Leu774Met (P-13) and p.Gly51Ser (P-2 and P-16) at the time of study sampling were 81, 84 and 76 years, respectively. In Caucasian populations, the number of carriers in cases and controls for the three variants were 5 versus 0 (p.Asp620Asn), 4 versus 1 (p.Leu774Met) and 3 versus 1 (p.Gly51Ser), respectively. In Asian descent populations, the respective numbers were 2 versus 0 (p.Asp620Asn), 2 versus 0 (p.Leu774Met) and 0 versus 1 (p.Gly51Ser). Most interestingly, two out of seven patients carrying the p.Asp620Asn variant presented without any family history for PD. This represents the first evidence for reduced penetrance of the respective variant initially attributed to autosomal dominant familial PD. We did not observe any carriers for one variant (p.Arg524Trp) in our cohort. Two non-synonymous variants (p.Met57Ile, p.Thr82Arg) failed genotyping. By collapsing the rare variants across different sites, we did not observe statistically significant increased risk for p.Leu774Met and p.Gly51Ser in our cohort (see online supplementary table S1).

Overall data synthesis for common variants

Out of three tag SNPs, one SNP (rs3218745) failed genotyping. We did not observe significant association for any of common variants with PD either with either fixed effect or random effect models (see online supplementary table S2). The OR ranged from 0.96 to 0.99 and tight 95% CIs excluded modest association effects. We observed no substantial heterogeneity for the two genotyped SNPs, and also the Q test was non-statistically significant for common SNPs. Moreover, examining the Caucasian or Asian populations separately did not change our results (data not shown).

Clinical features

All PD patients who carried potential pathogenic variants (p.Asp620Asn, p.Gly51Ser, p.Leu774Met) were clinically diagnosed with PD (Online supplementary clinical analysis data). A few of these (0.2%) affected individuals also have a positive family history. Affected individuals exhibited classical symptoms of PD (resting tremor, bradykinesia, rigidity) (table 2). The clinical diagnosis of PD was made by movement disorder specialists who used UK brain bank criteria for PD. Non-motor symptoms were present in the majority of PD patients carrying a pathogenic variant (table 2). Interestingly, hallucinations and dementia were also observed in one asymptomatic carrier suggesting clinical heterogeneity associated with VPS35. The identified healthy carriers have not shown any sign of PD as yet (table 2).

DISCUSSION

We performed the first multi-centre study to define the role of the VPS35 gene (PARK17) in PD by assessing the frequency of the reported non-synonymous variants in familial and sporadic PD patients from different populations worldwide. Among 15 383 subjects genotyped, we found a pathogenic relevance for p.Asp620Asn in different populations. Most interestingly, out of seven subjects who carry p.Asp620Asn, two have a negative family history. Therefore, our results provide additional evidence that VPS35 is a rare cause of familial as well as the common sporadic form of PD. In total, about 0.4% of PD cases in diverse population were due to disease-associated variant in the VPS35 gene. Our lack of supporting the role of common variants of the VPS35 gene in PD is consistent with recently published GWAS and also meta-analyses of GWAS of PD, as none of these highlighted the role of common variability in VPS35 gene as a risk factor for PD.^{11–15} The p.Asp620Asn

Table 1 Description of datasets contributed by each study site

Site	Country	N	Case	Control	Male (%)	Female (%)	Mean AAO	Mean Age at study	Diagnostic criteria
Annesi	Italy	394	197	197	204 (51.7%)	190 (48.2%)	61.5	63.7	UKPDBB
Brice	France	505	272	233	302 (59.8%)	203 (40.1%)	47.6	57.8	UKPDBB
Bozi	Greece	222	114	108	107 (48.1%)	115 (51.8%)	69.9	74.5	UKPDBB
Wszolek	USA	1518	692	826	794 (52.3%)	724 (47.6%)	64.4	71.7	UKPDBB
Garraux	Belgium	82	68	14	45 (54.8)	37 (45.1%)	62.1	69.6	UKPDBB
Hadjigeorgiou	Greece	714	357	357	379 (53.0%)	335 (46.9%)	63.4	63.7	UKPDBB
Jeon	Korea	749	408	341	314 (41.9%)	435 (58.0%)	57.6	NA	UKPDBB
Opala	Poland	629	352	277	340 (54.0%)	288 (45.7%)	50.2	68.1	UKPDBB
Lynch	Ireland	740	368	372	340 (45.9%)	400 (54.0%)	50.5	70.7	UKPDBB
Lin	Taiwan	320	160	160	160 (50%)	160 (50%)	62.0	70.8	UKPDBB
Facheris	Italy	181	114	67	86 (47.5%)	95 (52.4%)	63.0	NA	UKPDBB
Maraganore	USA	1024	801	223	600 (58.5%)	361 (35.3%)	59	74.7	Bower
Mellick	Australia	2024	1012	1012	1042 (51.4%)	981 (48.4%)	59	72.2	Bower
Morrison	England	1120	766	354	606 (54.1%)	514 (45.8%)	66.1	NA	UKPDBB
Mok	China	436	260	176	264 (60.5%)	170 (38.9%)	NA	63.5	UKPDBB
Aasly	Norway	1278	656	622	721 (56.4%)	557 (43.5%)	58.8	72.9	UKPDBB
Wirdefeldt	Sweden	299	83	216	147 (49.1%)	152 (50.8%)	65.8	71.4	Gelb
Van Broeckhoven	Belgium	1010	501	509	500 (49.5%)	509 (50.3%)	60.5	66.3	Pals/Gelb
Rogaeva	Canada	560	387	173	303 (54.1%)	257 (45.8%)	49.7	64.2	UKPDBB
Tan	Singapore	391	194	197	244 (62.4%)	147 (37.5%)	59.7	54.0	UKPDBB
Hattori	Japan	121	121	0	62 (51.2%)	59 (48.7%)	NA	NA	UKPDBB
Gasser/Sharma	Germany	760	760	0	479 (63.3%)	281 (36.9%)	58.9	NA	UKPDBB
Toda	Japan	306	227	79	161 (52.6%)	145 (47.3%)	57.8	65.1	UKPDBB
Total		15 383	8870	6513			59.5	67.6	

AAO, Age at onset; NA: Not applicable.

variant is located in the C-terminal region of the VPS35 protein pointing that subtle structural changes might influence the disease pathogenesis.³

The spectrum of proteins involved in PD aetiology has grown considerably. This includes proteins that are related to mitochondrial quality control (Parkin, PINK1 and DJ1), proteins involved in protein aggregation (SNCA) (Synuclein, MAPT) Microtubule associated protein Tau), and proteins

which are involved in sorting and degradation within endocytic and autophagy pathways ((VDAC) Voltage dependent anion channel, (GBA) Glucocerebrosidase gene, VPS35).^{16 17} So far, very little is known about the specific role of VPS35 in PD, except that it is hypothesised that it is involved in cargo recognition as part of a retrograde complex recycling membrane proteins from endosomes to the trans-Golgi network.^{3 4} Indeed, in vitro and in vivo studies strongly implicate the role of VPS35

Table 2 Clinical description of carriers of non-synonymous variants of vacuolar protein sorting 35 gene

Id	Ethnicity	Rare variant	Age at onset	Clinical signs	Bradykinesia	Rigidity	Tremor	Postural instability	L-dopa responsive	Non-motor symptoms	Family history
P-1	Caucasian	p.Asp620Asn	59	Classical PD	+	+	+	+	+	Negative	Negative
P-2	Caucasian	p.Gly51Ser	NA	Control	-	-	-	-	-	Negative	Negative
P-3	Caucasian	p.Gly51Ser	NAV	Classical PD	+	+	+	+	+	Dementia, visual hallucinations	Negative
P-4	Caucasian	p.Gly51Ser	55	Classical PD	+	+	+	+	+	Negative	Negative
P-5	Caucasian	p.Gly51Ser	49	Classical PD	+	+	+	+	+	Negative	Negative
P-6	Caucasian	p.Asp620Asn	37	Classical PD	+	+	+	+	+	Negative	Positive
P-7	Caucasian	p.Asp620Asn	59	Classical PD	+	+	+	+	+	Negative	Positive
P-8	Caucasian	p.Asp620Asn	55	Classical PD	+	+	+	+	+	Negative	Positive
P-9	Caucasian	p.Asp620Asn	66	Classical PD	+	+	+	+	+	Negative	Positive
P-10	Caucasian	p.Leu774Met	41	Classical PD	+	+	+	+	+	Negative	Positive
P-11	Caucasian	p.Leu774Met	65	Classical PD	+	+	+	+	+	Negative	Positive
P-12	Caucasian	p.Leu774Met	65	Classical PD	+	+	+	+	+	Disturbance of gait and balance	Positive
P-13	Caucasian	p.Leu774Met	NA	Control	-	-	-	-	NA	-	Negative
P-14	Caucasian	p.Leu774Met	44	Classical PD	+	+	+ Rest 1st sx	+	+	Autonomic dysfunction	Positive
P-15	Asian	p.Asp620Asn,p.Leu774Met	52	Classical PD	+	+	+	+	+	Negative	Negative
P-16	Asian	p.Gly51Ser		Control	-	-	-	-	-	-	Negative
P-17	Asian	p.Leu774Met	75	Classical PD	+	+	+	+	+	Negative	Negative
P-18	Asian	p.Asp620Asn	43	Classical PD	+	+	+	+	+	Mild cognitive impairment	Positive

NA, not applicable; NAV, not available; PD, Parkinson disease; + positive; -negative.

Genotype-phenotype correlations

gene in neurodegeneration. For example, reduced levels of VPS35 have been found in affected brain regions of Alzheimer disease (AD) patients¹⁸ and loss of VPS35 function has been shown to increase the levels of amyloid β and cause synaptic impairment in a mouse model of AD. Furthermore, variants in another member of the VPS family and substrate of retromer complex, SORL1, have been implicated in AD.¹⁹

In this study, we have focused only on non-synonymous variants identified by Zimprich and colleagues.³ Of note, we confirmed the pathogenic relevance of the p.Asp620Asn variant which was identified by both studies for familial cases and in sporadic PD. Recently, published studies also identified p.Asp620Asn mutations in PD,^{6, 20} thus providing support to the role of p.Asp620Asn in PD. In our study, clinically, the symptomatic carriers showed a broad spectrum of clinical phenotypes ranging from typical PD to (DLB) Dementia with Lewy body, so longitudinal evaluation of carriers at risk will provide unique information on the natural course of the disease caused by VPS35. Even though our data support the role of p.Asp620Asn variant in PD, given the fact that the frequency in diverse population is far below <1%, it is likely to be a rare cause of PD worldwide. Nevertheless, sequencing of families is encouraged for identifying additional missense variants which may provide mechanistic insight into the causes of PD.

Author affiliations

- ¹Department of Neurodegenerative diseases, Hertie-Institute for Clinical Brain Research and DZNE- German Center for Neurodegenerative Diseases, Tübingen
²Stanford Prevention Research Center, Department of Medicine and Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California, USA
³Department of Neurology, St Olavs Hospital and NTNU Trondheim, Trondheim, Norway
⁴Institute of Neurology, Department of Medical Sciences, University Magna Graecia, Catanzaro; Neuroimaging Research Unit, National Research Council, Catanzaro, Italy
⁵INSERM, UMR_S975, Université Pierre et Marie Curie-Paris, CNRS, UMR 7225, AP-HP, Pitié-Salpêtrière Hospital
⁶Cnrs, UMR 7225, Paris, France
⁷AP-HP Hôpital Pitié-Salpêtrière, Department of Genetics and Cytogenetics, Paris, France
⁸Neuropsychiatric Genetics Group, Department of Vertebrate Genomics, Max Planck Institute for Molecular Genetics, Berlin, Germany
⁹General Hospital of Syros, Syros, Greece
¹⁰'Hygeia' Hospital, Clinic of Neurodegenerative Disorders, Athens, Greece
¹¹2nd Neurology Clinic, University of Athens, 'Attikon' Hospital, Athens, Greece
¹²Department of Neurodegenerative Disorders, Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland
¹³Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB, Antwerp, Belgium
¹⁴Institute Born-Bunge, University of Antwerp, Antwerp, Belgium
¹⁵Department of Neurology, Antwerp University Hospital, Antwerp, Belgium.
¹⁶School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, City Hospital, Birmingham, UK
¹⁷Centre for Biomedicine, European Academy Bozen/Bolzano, Italy, Affiliated institute of the University of Lübeck, Lübeck, German
¹⁸Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada
¹⁹Human Genetic Centre, University Hospital of Liège, Liège, Belgium and Department of Neurology, General Central Hospital, Bolzano, Italy
²⁰Department of Neurology, Goethe University Frankfurt am Main, Frankfurt, Germany
²¹Department of Neurology, University of Thessaly and Institute of Biomedical Research and Technology, CERETETH, Larissa, Greece
²²Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan
²³Department of Neurology, Seoul National University Hospital, Seoul, Korea
²⁴Department of Neurology, Medical University of Warsaw, Warsaw, Poland
²⁵Department of Neurology, Jagiellonian University, Krakow, Poland
²⁶Department of Neurology, Johannes Gutenberg University, Mainz, Germany
²⁷Department of Neurology, Chushang Show-Chwan Hospital, Nantou and Chung-Shan Medical University Hospital, Taichung, Taiwan
²⁸The Dublin Neurological Institute at the Mater Misericordiae University Hospital, and Conway Institute, University College Dublin, Dublin, Ireland
²⁹Helmholtz Zentrum München, German Research Centre for Environmental Health (GmbH), Neuherberg, Germany

- ³⁰Movement Disorders Centre, and the Edmond J Safra Program in Parkinson's Disease, Toronto Western Hospital, University of Toronto, Toronto, Canada
³¹Department of Neurology, National Center Hospital of Neurology and Psychiatry, Tokyo, Japan
³²Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong
³³Department of Neurology, Medical University of Silesia, Katowice, Poland
³⁴Eskitis Institute for Cell and Molecular Therapies, Griffith University, Brisbane, Australia
³⁵Neurosciences Department, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
³⁶German Research Center for Environmental Health, Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany
³⁷Institute of Human Genetics, Technische Universität München, Munich, Germany
³⁸Department of Neurology, Medizinische Universität Wien, Vienna, Austria
³⁹Tanz Centre for Research in Neurodegenerative Diseases, Department of Medicine, University of Toronto, Toronto, Canada
⁴⁰Department of Neuroscience, Mayo Clinic, Jacksonville, Florida
⁴¹Divisions of Basic Neurosciences & Cell Biology, Biomedical Research Foundation of Academy of Athens, Athens, Greece
⁴²Division of Neurology/Molecular Brain Science, Kobe University Graduate School of Medicine, Kobe, Japan
⁴³University of Queensland Centre for Clinical Research, Herston, Australia
⁴⁴Department of Neurology, Singapore General Hospital, National Neuroscience Institute, Singapore
⁴⁵Department of Neurology, Mayo Clinic Jacksonville, USA
⁴⁶Epidemiology and Biostatistics and Department of Clinical Neuroscience, Karolinska Institutet
⁴⁷Department of Neurology, National Hospital Organization Tokyo Hospital, Tokyo, Japan
⁴⁸Department of Neurology, NorthShore University HealthSystem, Chicago, USA

Acknowledgements RS Boyle, MD (Princess Alexandra Hospital, Brisbane, Site Investigator); A Sellbach, MD (Princess Alexandra Hospital, Brisbane, Site Investigator); JD O'Sullivan, MD (Royal Brisbane and Women's Hospital Brisbane, Site Investigator); GT Sutherland, PhD (Eskitis Institute for Cell and Molecular Therapies, Griffith University, Nathan, QLD, Site Investigator); GA Siebert, MD (Eskitis Institute for Cell and Molecular Therapies, Griffith University, Nathan, QLD, Site Investigator); NNW Dissanayaka, MD (Eskitis Institute for Cell and Molecular Therapies, Griffith University, Nathan, QLD, Site Investigator); Christine Van Broeckhoven, PhD DSc (Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB; and Laboratory of Neurogenetics, Institute Born-Bunge; and University of Antwerp); Jessie Theuns, PhD (Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB; and Laboratory of Neurogenetics, Institute Born-Bunge; and University of Antwerp); David Crosiers, MD (Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB; and Laboratory of Neurobiology, Institute Born-Bunge; and University of Antwerp; and Department of Neurology, Antwerp University Hospital, Antwerp); Barbara Pickut, MD (Department of Neurology, Antwerp University Hospital, Antwerp); Sebastiaan Engelborghs, MD, PhD (Laboratory of Neurochemistry and Behaviour, Institute Born-Bunge; and University of Antwerp; and Department of Neurology and Memory Clinic, Hospital Network Antwerp, Middelheim and Hoge Beuken, Antwerp); Aline Verstraeten (Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB; and Laboratory of Neurogenetics, Institute Born-Bunge; and University of Antwerp); Peter P De Deyn, MD, PhD (Laboratory of Neurochemistry and Behaviour, Institute Born-Bunge; and University of Antwerp; and Department of Neurology and Memory Clinic, Hospital Network Antwerp, Middelheim and Hoge Beuken, Antwerp; and Department of Neurology and Alzheimer Research Center, University Medical Center Groningen, The Netherlands); Patrick Cras, MD, PhD (Laboratory of Neurobiology, Institute Born-Bunge; and University of Antwerp; Department of Neurology, Antwerp University Hospital, Antwerp). Funding: The research was in part supported by the Methusalem excellence program of the Flemish Government; a Centre of Excellence grant by the Special Research Fund of the University of Antwerp; the Research Foundation Flanders (FWO); the Agency for Innovation by Science and Technology Flanders (IWT); the Interuniversity Attraction Poles program (IAP) P6/43 of the Belgian Science Policy Office; the Belgian Parkinson Foundation; and the Foundation for Alzheimer Research (SAO/FRMA). DC is receiving a PhD fellowship of the FWO and AV of the IWT. Ekaterina Rogava, PhD (Tanz Centre for Research in Neurodegenerative Diseases, Department of Medicine, Division of Neurology, University of Toronto, ON, Canada, Site Investigator); Anthony E Lang, MD (Movement Disorders Centre, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, Site Investigator); Y Agid, MD (Inserm, Paris, From the French Parkinson's Disease Genetics Study Group, Site Investigator); M Anheim, MD (Inserm, Paris, From the French Parkinson's Disease Genetics Study Group, Site Investigator); A-M Bonnet, MD (Inserm, Paris, From the French Parkinson's Disease Genetics Study Group, Site Investigator); M Borg, MD (From the French Parkinson's Disease Genetics Study Group, Site Investigator); A Brice, MD (Paris, From the French Parkinson's Disease Genetics Study Group, Site Investigator); E Broussolle MD (From the French Parkinson's Disease Genetics Study Group, Site Investigator); JC Corvol MD (Inserm, Paris, From the

French Parkinson's Disease Genetics Study Group, Site Investigator); P Damier, MD (From the French Parkinson's Disease Genetics Study Group, Site Investigator); A Destée, MD (From the French Parkinson's Disease Genetics Study Group, Site Investigator); A Dürr, MD (Inserm U708, Paris, From the French Parkinson's Disease Genetics Study Group, Site Investigator); F Durif, MD (From the French Parkinson's Disease Genetics Study Group, Site Investigator); S Lesage, PhD (Inserm, Paris, From the French Parkinson's Disease Genetics Study Group, Site Investigator); E Lohmann, MD (Inserm, Paris, From the French Parkinson's Disease Genetics Study Group, Site Investigator); P Pollak, MD (From the French Parkinson's Disease Genetics Study Group, Site Investigator); O Rascol, MD (From the French Parkinson's Disease Genetics Study Group, Site Investigator); F Tison, MD (From the French Parkinson's Disease Genetics Study Group, Site Investigator); C Tranchant, MD (From the French Parkinson's Disease Genetics Study Group, Site Investigator); F Viallet, MD (From the French Parkinson's Disease Genetics Study Group, Site Investigator); M Vidali, MD (Inserm, Paris, From the French Parkinson's Disease Genetics Study Group, Site Investigator); Christophe Zourio, MD (Inserm U708, Paris, From the French Parkinson's Disease Genetics Study Group, Site Investigator); Philippe Amouyel, MD (Inserm U744, Lille, Site Investigator); Marie-Anne Lohiot, MD (Inserm UMR5775, Paris, Site Investigator); Eugénie Mutez, MD (Inserm UMR837, Service de Neurologie et de Pathologie du Mouvement CHRU de Lille, Univ Lille Nord de France, Site Investigator); Aurélie Duflo, MD (UMR837 Inserm-Univ Lille 2, CHRU de Lille, Site Investigator); Jean-Philippe Legendre, MD (Service de Neurologie et Pathologie du Mouvement, Clinique de Neurologie du CHU de Lille, Site Investigator); Nawal Wauquier, MD (Service de Neurologie et Pathologie du Mouvement, Clinique de Neurologie du CHU de Lille, Site Investigator); Thomas Gasser MD (Department of Neurology, University Hospital Tuebingen, Site Investigator); Olaf Riess MD (Department of Neurology, University Hospital Tuebingen, Site Investigator); Christine Klein, MD (Section of Clinical and Molecular Neurogenetics at the Department of Neurology, University of Lübeck, Site Investigator); Ana Djarmati, PhD (Department of Neurology, University of Lübeck, Site Investigator); Johann Hagenah, MD (Department of Neurology, University of Lübeck, Site Investigator); Katja Lohmann, PhD (Section of Clinical and Molecular Neurogenetics at the Department of Neurology, University of Lübeck, Site Investigator); Georg Auburger, MD (Department of Neurology, Goethe University Frankfurt am Main, Germany, Site Investigator); Rüdiger Hilker, MD (Department of Neurology, Goethe University Frankfurt am Main, Germany, Site Investigator); Simone van de Loo, MD (Department of Neurology, Goethe University Frankfurt am Main, Germany, Site Investigator); Efthimios Dardiotis, MD (Department of Neurology, Faculty of Medicine, University of Thessaly and Institute of Biomedical Research & Technology, CERETETH, Larissa; Site Investigator); Vaia Tsimourtou, MD (Department of Neurology, Faculty of Medicine, University of Thessaly, Larissa, Site Investigator); Styliani Ralli, MD (Department of Neurology, Faculty of Medicine, University of Thessaly, Larissa, Site Investigator); Persa Kountra, MD (Department of Neurology, Faculty of Medicine, University of Thessaly, Larissa, Site Investigator); Gianna Patramani, MD (Department of Neurology, Faculty of Medicine, University of Thessaly, Larissa, Site Investigator); Cristina Vogiatzi, MD (Department of Neurology, Faculty of Medicine, University of Thessaly, Larissa, Site Investigator); Nobutaka Hattori, MD, PhD (Department of Neurology, Juntendo University School of Medicine, Tokyo, Site Investigator); Hiroyuki Tomiyama, MD, PhD (Department of Neurology, Juntendo University School of Medicine, Tokyo, Site Investigator); Manabu Funayama, PhD (Department of Neurology, and Research Institute for Diseases of Old Age, Graduate School of Medicine, Juntendo University, Tokyo, Site Investigator); Hiroyo Yoshino, PhD (Research Institute for Diseases of Old Age, Graduate School of Medicine, Juntendo University, Tokyo, Site Investigator); Yuanzhe Li MD, PhD Research Institute for Diseases of Old Age, Graduate School of Medicine, Juntendo University, Tokyo, Site Investigator); Yoko Imamichi (Department of Neurology, Juntendo University School of Medicine, Tokyo, Site Investigator); Tatsushi Toda, MD (Division of Neurology/Molecular Brain Science, Kobe University Graduate School of Medicine, Kobe, Japan, Site Investigator); Wataru Satake, MD, PhD (Division of Neurology/Molecular Brain Science, Kobe University Graduate School of Medicine, Kobe, Japan, Site Investigator); Tim Lynch, MD (The Dublin Neurological Institute at the Mater Misericordiae University Hospital, Clinical Investigator at the Conway Institute, University College Dublin, Ireland, Site Investigator); J Mark Gibson, MD (Department of Neurology, Royal Victoria Hospital, Belfast, Ireland, Site Investigator); Enza Maria Valente, MD, PhD (IRCCS, Casa Sollievo della Sofferenza Hospital, Mendel Institute, San Giovanni Rotondo, Site Investigator); Alessandro Ferraris, MD (IRCCS, Casa Sollievo della Sofferenza Hospital, Mendel Institute, San Giovanni Rotondo, Site Investigator); Bruno Dallapiccola, MD (Mendel Institute, Casa Sollievo della Sofferenza Hospital, Rome, Site Investigator); Tamara Ialongo, MD, PhD (Institute of Neurology, Catholic University, Rome, Site Investigator); Laura Brighina, MD, PhD (Department of Neurology, Ospedale San Gerardo, Monza, Italy, Site Investigator); Barbara Corradi, PhD (Department of Paediatrics, University of Milano-Bicocca, Monza, Site Investigator); Roberto Piolti, MD (Department of Neurology, Ospedale San Gerardo, Monza, Italy, Site Investigator); Patrizia Tarantino, PhD (Institute of Neurological Sciences, National Research Council, Site Investigator); Ferdinando Annesi, PhD (Institute of Neurological Sciences, National Research Council, Site Investigator); Beom S Jeon, MD, PhD (Department of Neurology, Seoul National University Hospital, Site Investigator); Sung-Sup Park, MD, PhD (Department of Laboratory Medicine, Seoul National University Hospital, Site Investigator); J Aasly, MD

(Department of Neurology, University of Trondheim, Norway, Site Investigator); Grzegorz Opala, MD, PhD (Department of Neurology, Aging, Degenerative and Cerebrovascular Disorders, Medical University of Silesia, Katowice; Site Investigator); Barbara Jasinska-Myga, MD, PhD (Department of Neurology, Aging, Degenerative and Cerebrovascular Disorders, Medical University of Silesia, Katowice, Site Investigator); Gabriela Klodowska-Duda, MD, PhD (Department of Neurology, Aging, Degenerative and Cerebrovascular Disorders, Medical University of Silesia, Katowice, Site Investigator); Magdalena Boczarska-Jedynak, MD, PhD (Department of Neurology, Aging, Degenerative and Cerebrovascular Disorders, Medical University of Silesia, Katowice, Site Investigator); Eng King Tan, MD, PhD (National Medical and Biomedical Research Councils, and the Duke-NUS Graduate Medical School, Singapore Millennium Foundation, Site Investigator); Andrea Carmine Belin, PhD (Department of Neuroscience, Karolinska Institutet, Stockholm, Site Investigator); Lars Olson, MD (Department of Neuroscience, Karolinska Institutet, Stockholm, Site Investigator); Dagmar Galter, PhD (Department of Neuroscience, Karolinska Institutet, Stockholm; Site Investigator); Marie Westerlund, PhD (Department of Neuroscience, Karolinska Institutet, Stockholm, Site Investigator); Olof Sydow, PhD (Department of Clinical Neuroscience, Karolinska University Hospital, Stockholm; Site Investigator); Christer Nilsson, MD, PhD (Department of Geriatric Psychiatry, Lund University; Site Investigator); Andreas Puschmann, MD (Department of Neurology, Lund University Hospital, Department of Geriatric Psychiatry, Lund University, Site Investigator); JJ Lin, MD (Department of Neurology, Cushing Show-Chwan Hospital, Taiwan, Site Investigator); Demetrius M Maraganore, MD (Department of Neurology, NorthShore Health Systems, Chicago, IL, Site Investigator); J Eric Ahlskog PhD, MD (Department of Neurology, Mayo Clinic, Rochester, MN, USA, Site Investigator); Mariza de Andrade, PhD (Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA, Site Investigator); Timothy G Lesnick, MS (Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA, Site Investigator); Walter A Rocca, MD, MPH (Departments of Neurology and Health Sciences Research, Mayo Clinic, Rochester, MN, USA, Site Investigator); Harvey Checkoway, PhD (Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, Site Investigator); Owen A Ross PhD (Division of Neuroscience, Mayo Clinic, Jacksonville, USA, Site Investigator); Zbigniew K Wszolek, MD (Department of Neurology, Mayo Clinic, Jacksonville, FL, Site Investigator); Ryan J Uitti, MD (Department of Neurology, Mayo Clinic, Jacksonville, FL, Site Investigator).

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A multi-centre clinico-genetic analysis of the VPS35 gene in Parkinson disease indicates reduced penetrance for disease-associated variants

Manu Sharma, John P A Ioannidis, Jan O Aasly, Grazia Annesi, Alexis Brice, Lars Bertram, Maria Bozi, Maria Barcikowska, David Crosiers, Carl E Clarke, Maurizio F Facheris, Matthew Farrer, Gaetan Garraux, Suzana Gispert, Georg Auburger, Carles Vilariño-Güell, Georgios M Hadjigeorgiou, Andrew A Hicks, Nobutaka Hattori, Beom S Jeon, Zygmunt Jamrozik, Anna Krygowska-Wajs, Suzanne Lesage, Christina M Lill, Juei-Jueng Lin, Timothy Lynch, Peter Lichtner, Anthony E Lang, Cecile Libioulle, Miho Murata, Vincent Mok, Barbara Jasinska-Myga, George D Mellick, Karen E Morrison, Thomas Meitner, Alexander Zimprich, Grzegorz Opala, Peter P Pramstaller, Irene Pichler, Sung Sup Park, Aldo Quattrone, Ekaterina Rogaeva, Owen A. Ross, Leonidas Stefanis, Joanne D Stockton, Wataru Satake, Peter A Silburn, Tim M Strom, Jessie Theuns, Eng- King Tan, Tatsushi Toda, Hiroyuki Tomiyama, Ryan J Uitti, Christine Van Broeckhoven, Karin Wirdefeldt, Zbigniew Wszolek, Georgia Xiromerisiou, Harumi S Yomono, Kuo-Chu Yueh, Yi Zhao, Thomas Gasser, Demetrius Maraganore, Rejko Krüger and on behalf of GEOPD consortium

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