RESEARCH PAPER

The Val158Met COMT polymorphism is a modifier of the age at onset in Parkinson’s disease with a sexual dimorphism

Stephan Klebe, Jean-Louis Golmard, Michael A Nalls, Mohamad Saad, Andrew B Singleton, Jose M Bras, John Hardy, Javier Simon-Sanchez, Peter Heutink, Gregor Kuhlenbäumer, Rim Charfi, Christine Klein, Johann Hagenah, Thomas Gasser, Isabel Wueterst, Suzanne Lesage, Delia Lorenz, Günther Deuschl, Franck Durif, Pierre Pollak, PhilippeDamier, François Tison, Alexandra Durr, Philippe Amouyel, Jean-Charles Lambert, Christophe Tzourio, Cécilia Maubaret, FannyCharbonnier-Beaupeul, Khadija Tahiri, Marie Vidalhiet, Maria Martinez, Alexis Brice, Jean-Christophe Corvol, French Parkinson’s Disease Genetics Study Group and the International Parkinson’s Disease Genomics Consortium (IPDGC)

ABSTRACT

The catechol-O-methyltransferase (COMT) is one of the main enzymes that metabolise dopamine in the brain. The Val158Met polymorphism in the COMT gene (rs4680) causes a trinodal distribution of high (Val/Val), intermediate (Val/Met) and low (Met/Met) enzyme activity. We tested whether the Val158Met polymorphism is a modifier of the age at onset (AAO) in Parkinson’s disease (PD). The rs4680 was genotyped in a total of 16 609 subjects from five independent cohorts of European and North American origin (5886 patients with PD and 10 723 healthy controls). The multivariate analysis for comparing PD and control groups was based on a stepwise logistic regression, with gender, age and cohort origin included in the initial model. The multivariate analysis of the AAO was a mixed linear model, with genotype and gender considered as fixed effects and cohort and cohort-gender interaction as random effects. COMT genotype was coded as a quantitative variable, assuming a codominant genetic effect. The distribution of the COMT polymorphism was not significantly different in patients and controls (p=0.22). The Val allele had a significant effect on the AAO with a younger AAO in patients with the Val/Val (57.1±13.9, p=0.03) than the Val/Met (57.4±13.9) and the Met/Met genotypes (58.3±13.5). The difference was greater in men (1.9 years between Val/Val and Met/Met, p=0.007) than in women (0.2 years, p=0.81). Thus, the Val158Met COMT polymorphism is not associated with PD in the Caucasian population but acts as a modifier of the AAO in PD with a sexual dimorphism: the Val allele is associated with a younger AAO in men with idiopathic PD.

INTRODUCTION

Parkinson’s disease (PD) is a neurodegenerative disorder characterised by the loss of dopaminergic neurons in the mesencephalon. The diagnosis of PD is usually made when patients first notice symptoms of motor dysfunction (bradykinesia, tremor and rigidity) that are related to loss of the dopaminergic innervation in the striatum. However, the dopaminergic deficiency in the mesencephalon remains clinically silent until the concentration of dopamine has decreased by 60–80% in the striatum, and until 30–40% loss of dopaminergic neurons has been reached (1–7). Compensatory mechanisms may thus be involved to explain this delay in the occurrence of motor symptoms.

In the central nervous system, two main enzymes, the monoamine oxidase B (MAOB) and the catechol-O-methyltransferase (COMT) metabolise dopamine. The human COMT gene (OMIM 116790) is localised on chromosome 22q11.2. The distribution of COMT activity in the population and in families indicates that it is regulated by a single autosomal locus with two codominant alleles. The substitution of valine (Val) by methionine (Met) at codon 158 (Val158Met) in the membrane-bound isofrom, corresponding to codon 108 in the soluble form, results in a trimodal distribution of high, low and intermediate enzymatic activity. COMT activity is threfold to fourfold higher in the liver and red blood cells of 158Val patients than in those with the 158Met variant. There are ethnic differences in the distribution of the Val158Met genotype. About 25% of the Caucasian population is homozygous for the low activity variant (Met/Met), 25% is homozygous for the high activity variant (Val/Val) and 50% has the intermediate activity variant (Val/Met). The influence of the COMT Val158Met polymorphism on non-motor symptoms in PD, particularly cognitive functions, has been studied.

For numbered affiliations see end of article.

Correspondence to Dr Jean-Christophe Corvol, Centre d’Investigation Clinique, Institut du Cerveau et de la Moelle épinière, Hôpital de la Pitié-Salpêtrière, 47 boulevard de l’Hôpital, Paris 75651 Cedex 13, France; jean-christophe.corvol@psl.aphp.fr.

Received 5 November 2012
Revised 4 January 2013
Accepted 7 January 2013
Published Online First 13 February 2013
but little is known about its effect on motor symptoms. In the present study, we hypothesise that COMT activity might modulate the age at onset (AAO) of motor symptoms in PD by modifying the bioavailability of the remaining endogenous dopamine in the striatum. Using the COMT Val158/108Met polymorphism as a surrogate marker of enzyme activity, we performed an association study in 16,609 patients and controls of European and North American origin.

**PATIENTS AND METHODS**

**French samples**

Subjects with PD (n=1,031) were recruited through the French network for the study of Parkinson’s disease genetics associating 15 university hospitals across France. All patients were of European origin. Definite and probable PD was defined according to the UK Parkinson’s Disease Society Brain Bank (UKPDSBB).12 The healthy controls (n=2,061) of the French sample came from either the French Three-City (3C) cohort (n=1933)13 or the Parkinson’s disease genetics network (n=128). The participants of the 3C cohort were non-institutionalised subjects over 65 years of age, randomly selected from the electoral rolls of three French cities. The control subjects were matched for gender with patients with PD.

**German samples**

The German samples consisted of three independent cohorts (Kiel, Lübeck and Tübingen). Patients with PD (n=648) and healthy controls (n=688) from the Kiel sample were from the Population Based Assessment of Genetic Risk Factors for PD study performed in northern Germany in cooperation with the Populationsgenetik (POPGEN) biobank.14 All participating patients with PD were diagnosed by board certified neurologists according to the UKPDSBB Criteria.12 Controls (n=688), also obtained by POPGEN, were matched to the cases by gender and geographical origin and were screened to confirm the absence of PD. The Lübeck sample consisted of 525 cases and 223 healthy controls collected in specialised outpatient clinics. All patients underwent a detailed neurological examination by a movement disorder specialist and the diagnosis of PD was established clinically according to the UKPDSBB.12 The controls underwent the same neurological examination as the patients. The PD cases (n=662) for the Tübingen cohort were collected by movement disorders specialists at the Universities of Munich and Tübingen, according to the UKPDSBB.12 Sample collection from controls (n=767) was performed as part of the Prospective validation of risk markers for the development of idiopathic Parkinson syndrome (PRIPS) study in Tübingen.

**International Parkinson’s Disease Genomics Consortium**

Genome-wide association studies-based data from three contributing cohorts from the International Parkinson’s Disease Genomics Consortium was used in this study and have been described in detail elsewhere.15–16 This includes 937 cases of PD and 3033 controls from the US samples from the National Institute on Aging cohort, 744 cases and 2019 controls from the Dutch cohort, and 1648 cases and 2699 controls from the UK cohort.17–19

All these studies were carried out in accordance with the Declaration of Helsinki and the rules for clinical good practice. All participants gave their informed consent. The local Ethical Committees approved the studies.

**AAO definition**

AAO was systematically determined at the time of inclusion by a retrospective interview. The AAO was defined as the first PD-related motor symptom (akinesia, tremor or rigidity) experienced by the patient for the French, Lübeck and Tübingen cohorts, and by the age at which PD was first diagnosed for the Kiel sample and the International Parkinson’s Disease Genomics Consortium cohorts.

**Genotyping**

The COMT polymorphism G185A (rs4680) was analysed by an allelic discrimination Taqman assay (Applied Biosystems PRISM 7900 sequence detection system, Applied Biosystems, Foster City, USA) for the German samples or extracted from DNA array studies as described elsewhere.15 16 20–24

**Statistical analysis**

Descriptive statistics used numbers and percentages as qualitative variables and means and SDs as quantitative variables.

Relationships between qualitative variables were tested using χ² tests and comparisons between means of quantitative variables were performed using Student t tests for two groups and unbalanced analysis of variance (ANOVA) for more than two groups. The multivariate analysis for comparing PD and control groups was based on a stepwise logistic regression, with all variables included in the initial model and variables statistically significant with p<0.05 by the Wald test retained in the final model. The multivariate analysis of the AAO was first based on a mixed linear model, with the COMT genotype and gender considered as fixed effects and cohort and cohort-gender interaction considered as random effects. In a second step, two distinct models were fitted, one for men and one for women, with the COMT genotype as the fixed effect and the cohort as the random effect. In all mixed linear models, the COMT genotype was coded as a quantitative variable, namely as the number of ‘L’ alleles. Hardy-Weinberg equilibrium was tested using χ² tests in each sample. All tests were two-sided, with a p value of 0.05 considered statistically significant. Computations were performed using the SAS V9 statistical package.

**RESULTS**

**Characteristics of patients and controls**

A total of 17,665 subjects were available (6177 patients with PD and 11,488 controls). Due to insufficient DNA quantity or quality or missing clinical information 1056 specimens were excluded for further analysis. Finally, 16,609 subjects were genotyped for the rs4680 polymorphism and included in the analysis (5886 patients with PD and 10,723 healthy controls).

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Sex ratio AAO</td>
<td>n</td>
</tr>
<tr>
<td>All</td>
<td>5886 1.5 57.6±13.8 10723 1.01 60.0±10.1</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>937 1.5 57.8±13.2 3033 0.89 63.3±10.1</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>1648 1.4 64.2±12.4 2699 1.07 53.0±0.0</td>
<td></td>
</tr>
<tr>
<td>NL</td>
<td>744 1.8 55.6±11.8 2019 0.79 55.7±5.8</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>1031 1.3 48.4±13.2 2061 1.20 73.0±6.4</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>1526 1.5 57.3±13.0 911 1.14 50.2±15.7</td>
<td></td>
</tr>
</tbody>
</table>

AAO, age at onset; n, number of subjects; NL, Netherlands; Sex ratio, male/female; PD, Parkinson’s disease; US, North-American.

The characteristics of subjects in the five cohorts are summarised in table 1. The mean AAO for patients with PD was 57.6±13.8 years. Cohorts of patients with PD were significantly different in terms of AAO (p<0.001) and sex ratio (p=0.04). The mean AAO was also significantly different between gender (male 57.1±13.7, female 58.3±13.9, p=0.001). Subsequent analyses thus included gender and cohorts in the multivariate model.

### Distribution of the COMT polymorphism

The distribution of the Val158Met polymorphism in the dataset is described in table 2. The distribution of the single nucleotide polymorphism (SNP) was in Hardy-Weinberg equilibrium in patients (p=0.44) and controls groups (p=0.25). The distribution of genotypes (Val/Val, Val/Met and Met/Met) was similar and not significantly different in patients and controls (table 2, p=0.22). However, genotype distributions differed significantly among cohorts (p<0.001). The multivariate analysis including gender, cohorts and the age of PD and controls in the model found no significant association between the Val158Met polymorphism and PD (p=0.22). Altogether, these results failed to find an association between rs4680 and PD in a large population of Caucasian patients with PD and controls.

### AAO and COMT polymorphism

The AAO was analysed assuming a genetic codominant model for the Val158Met COMT polymorphism in accordance with its codominant effect on the enzyme activity. A significant difference of AAO was found for the French (47.9±13.3 for Val/Val compared with 50.2±13.1 for Met/Met, p=0.04) and the US presence of AAO was found for the Val/Val compared with the Met/Met genotype (57.1±13.9 vs 58.3±13.5, p=0.017). Interestingly, this difference was higher in male patients (56.0±14.1 for Val/Val compared with 57.9±13.6 for Met/Met, p=0.007) than in female patients (58.6±13.4 for Val/Val compared with 58.8±13.3 for Met/Met, p=0.81) (table 3).

### DISCUSSION

This is the largest study in which the COMT polymorphism rs4680 (Val158Met) was genotyped in PD in 16 609 patients and controls from different European and North American samples. We show that the rs4680 polymorphism is a genetic modifier of the AAO in patients with idiopathic PD. Our results suggest a codominant effect of the COMT Val158Met polymorphism resulting in a modification of the AAO by 1.2 years between extreme genotypes (Val/Val and Met/Met). This effect was significant in men but not in women with a 1.9 years difference between extreme genotypes in men. This modifying effect was not associated with an increased risk of PD associated with the Val158Met polymorphism. This result confirms, in a larger cohort, the absence of association between this polymorphism and PD risk in the Caucasian population.7 25–27 In the French and US samples we revealed a significant earlier AAO associated with the Val/Val genotypes. In the remaining samples from Germany, the Netherlands and the UK no significant result has been shown. A possible explanation might be that these samples were underpowered.

The effect of the COMT Val158Met polymorphism on AAO might be explained by a difference of metabolism of the endogenous dopamine in the striatum at disease onset. Indeed, patients carrying the Val158 allele (Val/Val and Met/Met) may have a reduced dopamine bioavailability because of a higher enzyme activity leading to earlier motor symptoms. Conversely, poor metabolisers (Met/Met) may have a greater dopamine bioavailability delaying their motor symptoms. The inverse U curve effect of dopamine concentration in the frontal cortex28 was elegantly validated in studies of working memory in healthy and schizophrenic patients demonstrating that the Val158Met COMT polymorphism has indeed functional consequences on brain function.29 30 In PD, studies on the impact of the Val158Met polymorphism on non-motor symptoms have produced conflicting results.7–11 No evidence was found for an association between the Val158Met genotype and daytime sleepiness or on neuropsychological measures of attention and executive function.9 10 Other studies showed that the genotype directly affects executive function in early stage PD. Val/Val patients have less frontoparietal activation on fMRI11 and better performance on executive tasks.8 11 A pharmacogenetic study showed that the COMT polymorphism determines the acute response to entacapone,31 although the motor response to levodopa alone was not modified by the COMT polymorphism.31 32 These results collectively show that the COMT polymorphism modifies the PD phenotype. Considering its frequency, it might have to be taken into account in the clinical management of patients with PD.

An interesting result in our study was the gender difference of the COMT genotype effect on AAO. The AAO was not significantly different in women whereas it was 1.9 years earlier in men with an earlier AAO for those carrying the Val158 allele, corresponding to the high enzyme activity (table 3, p=0.04). The multivariate analysis confirmed the significant association of the AAO with the COMT polymorphism when cohorts and gender were included in the model (p=0.03). The difference of AAO was 1.2 years earlier for patients with the Val/Val genotype compared with patients with the Met/Met genotype (57.1±13.9 vs 58.3±13.5, p=0.017). Interestingly, this difference was higher in male patients (56.0±14.1 for Val/Val compared with 57.9±13.6 for Met/Met, p=0.007) than in female patients (58.6±13.4 for Val/Val compared with 58.8±13.3 for Met/Met, p=0.81) (table 3).

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**Table 2** Distribution of the COMT Val158Met polymorphism in PD and controls

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Total (%) (n)</th>
<th>Control (%) (n)</th>
<th>PD (%) (n)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val/Val</td>
<td>23.7 (3943)</td>
<td>23.6 (2526)</td>
<td>24.1 (1417)</td>
<td>0.22</td>
</tr>
<tr>
<td>Val/Met</td>
<td>49.5 (8214)</td>
<td>49.5 (5303)</td>
<td>49.5 (2911)</td>
<td></td>
</tr>
<tr>
<td>Met/Met</td>
<td>26.8 (4452)</td>
<td>27.0 (2894)</td>
<td>26.5 (1558)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3** Age at onset in patients with PD according to COMT Val158Met genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
<th>Univariate p value</th>
<th>Multivariate p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met/Met</td>
<td>58.3±13.3</td>
<td>57.9±13.6</td>
<td>58.8±13.3</td>
<td>0.041</td>
<td>0.026*</td>
</tr>
<tr>
<td>Val/Val</td>
<td>57.1±13.9</td>
<td>57.1±13.9</td>
<td>57.1±13.9</td>
<td>0.013</td>
<td>0.007**</td>
</tr>
<tr>
<td>Val/Met</td>
<td>57.9±13.6</td>
<td>57.7±14.3</td>
<td>58.6±13.4</td>
<td>0.29</td>
<td>0.81**</td>
</tr>
</tbody>
</table>

*Multivariate model including cohorts and gender as cofactors.
**Multivariate model including cohorts as cofactor.
Val/Val: homozygous for the Val158 allele; Val/Met: heterozygous; Met/Met: homozygous for the Met158 allele.
COMT: catechol-O-methyltransferase; PD: Parkinson’s disease.
with the Val/Val genotype compared with the Met/Met genotype. A sexually dimorphic autosomal genetic association of the COMT gene has been well-recognised in psychiatric disorders but has not yet been described in PD. One of the best-replicated findings was the association of low enzymatic activity with obsessive-compulsive disorder in men, but not in women.\textsuperscript{13–15} In postmortem studies, the dorsolateral prefrontal cortex of women had lower COMT activity than men.\textsuperscript{16} Further evidence for gender differences comes from COMT knockout mice (COMT\textsuperscript{-/-}).\textsuperscript{23} In this model dopamine levels in the frontal cortex are significantly increased in male COMT\textsuperscript{-/-} mice compared with wild-type mice, but not in female COMT\textsuperscript{+/+} mice. Sex hormones, especially oestrogen, probably contribute to explain gender differences. Oestrogens inhibit COMT mRNA expression in cells expressing oestrogen receptors.\textsuperscript{38} However, the oestrogen hypothesis might only be a part of the explanation of the gender dimorphism in our study because (1) oestrogen levels fall in post-menopausal women, the age at which PD commonly occurs and (2) in mid-age men the COMT protein and activity levels rise considerably,\textsuperscript{39} despite steady oestriol levels within this period.\textsuperscript{40} Bearing this in mind further pathophysiological mechanism could be responsible for the sexual dimorphism like additional gene implication or epigenetic regulation.\textsuperscript{41} A candidate gene involved in gender differences could be the monoamine oxidase B (MAOB; OMIM 309860), an X linked gene, which also participates in dopamine metabolism. The MAOB brain activity increases with age\textsuperscript{42} and its activity is regulated by epigenetic factors.\textsuperscript{43} Different SNPs of the MAOB\textsuperscript{44} and the combination of genotypes at risk for the MAOB and the COMT gene\textsuperscript{45} were suspected to be associated with PD. Interestingly, one MAOB SNP (rs1799836) was available in French patients with PD (n=992). In this subset, no significant association was found between AAO and this MAOB SNP either alone or in combination with the COMTrs4680 (data not shown).

Our study may have some limitations although statistical biases were carefully avoided by performing multivariate analyses adjusting for cohort origin and gender. Because non-motor—and non-dopaminergic symptoms—may precede motor symptoms in PD, disease onset might not adequately reflect dopaminergic denervation in the striatum that might be modified by the COMT. Finally, other environmental modifiers, like tobacco, are also likely to contribute to the development of PD symptoms but environmental factors were not available in our dataset. Genetic forms of PD as well as genetic susceptibility factors such as mutations in the galactocerebrosidase gene were not systematically screened. Indeed, an association between heterozygous galactosylations in the galactocerebrosidase gene were not systematically also likely to contribute to the development of PD symptoms but adjusting for cohort origin and gender. Because non-motor...
Birmingham NHS Foundation Trust, Birmingham B15 2TH; Ese Mudanohou: Neurogenetics Unit, UCL Institute of Neurology/National Hospital for Neurology and Neurosurgery, Queen Square, London, UK; Sean O’Sullivan: Queen Square Brain Bank for Neurological Disorders, Institute of Neurology, University College London, London, UK; Laura F. Crook: Parkinson’s Centre for Excellence, University of Sheffield, Sheffield, UK; Douglass Atkin: Genetics, Garvan Institute of Medical Research, Sydney, Australia; Nick Smeets: MRC Centre for Neurodegenerative Diseases, University of Cambridge, Cambridge, UK; Marijn Otten: Department of Neurology, University ofTuebingen, Tuebingen, Germany; Marti Pithon: Welcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7UL, UK; Joel S Perlmutter: Department of Psychiatry, Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, USA; Hijnar Petursson: deCODE genetics, Sturlugata 8, IS-101 Reykjavik, Iceland, Department of Medical Genetics, Institute of Human Genetics, University of Iceland, Reykjavik, Iceland; Peter Heutink: Department of Neurology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Simon Ryten: Department of Molecular Neurosciences, UCL Institute of Neurology, Queen Square, London, WICN 3BQ; Stephen Sawcer: Department of Clinical Neurosciences, Addenbrooke’s hospital, Hills Road, Cambridge, CB2 0QQ, UK; Anthony Schapira: Department of Neurology, UCL Institute of Neurology, Royal Free Hospital, Rowland Road, London NW3 2PF, UK; Hennie Scheffer: Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Karen Shaw: Queen Square Brain Bank for Neurological Disorders, Institute of Neurology, University College London, London, UK; Ira Shoulson: Department of Neurology, University of Rochester, Rochester, New York 14620, USA; Ellen Sidransky: Section on Molecular Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, USA; Rohan de Silva: Department of Molecular Neurosciences, UCL Institute of Neurology, Queen Square, London, WCIN 3BQ; Colin Smith: Department of Pathology, Wilkie Building, Teviot Place, Edinburgh, EH8 9AG; Chris CA Spencer: Welcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7UL, UK; Hreinn Stefansson: deCODE genetics, Sturlugata 8, IS-101 Reykjavik, Iceland; Stacy Steinberg: deCODE genetics, Sturlugata 8, IS-101 Reykjavik, Iceland; Joanna D Stockton: School of Clinical and Experimental Medicine, University of Birmingham, Edgbaston, Birmingham B15 2TT; Amy Strange: Welcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7UL, UK; Zhan Su: Welcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7UL, UK; Kevin Talbot: University of Oxford, Department of Clinical Neurology, John Radcliffe Hospital, Oxford OX3 9DU, UK; Carter Thom: Research Department for Neurodegenerative Diseases, University of California, Sunnyvale, California, USA; Awaizeh Tashakkori-Ghanbari: Welcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK; François Tison: Service de Neurologie, Hôpital Haut-Lévêque, Pessac, France; Justin Pearson: MRC Centre for Neuropsychiatric Genetics and Genomics, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK; André G Uitterlinden: Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands, Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands; Patrick Heutink: Department of Medical Genetics, VU University Medical Centre, Amsterdam, The Netherlands; Mîna Ryten: Department of Molecular Neurosciences, UCL Institute of Neurology, Queen Square, London, WCIN 3BQ; Stephen Sawcer: Department of Clinical Neurosciences, Addenbrooke’s hospital, Hills Road, Cambridge, CB2 0QQ, UK; Anthony Schapira: Department of Neurology, UCL Institute of Neurology, Royal Free Hospital, Rowland Road, London NW3 2PF, UK; Hennie Scheffer: Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Karen Shaw: Queen Square Brain Bank for Neurological Disorders, Institute of Neurology, University College London, London, UK; Ira Shoulson: Department of Neurology, University of Rochester, Rochester, New York 14620, USA; Ellen Sidransky: Section on Molecular Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, USA; Rohan de Silva: Department of Molecular Neurosciences, UCL Institute of Neurology, Queen Square, London, WCIN 3BQ; Colin Smith: Department of Pathology, Wilkie Building, Teviot Place, Edinburgh, EH8 9AG; Chris CA Spencer: Welcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7UL, UK; Hreinn Stefansson: deCODE genetics, Sturlugata 8, IS-101 Reykjavik, Iceland; Stacy Steinberg: deCODE genetics, Sturlugata 8, IS-101 Reykjavik, Iceland; Joanna D Stockton: School of Clinical and Experimental Medicine, University of Birmingham, Edgbaston, Birmingham B15 2TT; Amy Strange: Welcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7UL, UK; Zhan Su: Welcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7UL, UK; John Hardy: Department of Molecular Neurosciences, UCL Institute of Neurology, Queen Square, London, WCIN 3BQ; Peter Heutink: Department of Clinical Neurogenetics, Section of Medical Genomics, VU University Medical Centre, Amsterdam, The Netherlands; Alexis Broix: INSERM, UMR 5975 (formerly UMR 6279), Paris, France; Charles Durrant: Centre de Recherche de l’Institut du Cerveau et de la Moelle épinière, UMR 5975, Paris, France, CNRS, UMR 7225, Paris, France, AP-HP, Pitie-Salpêtrière Hospital, Department of Genetics and Cyto genetics, Paris, France; Thomas Gasser: Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tuebingen, Germany; Alexander W Wood: UCL Institute of Neurology, London WC1E 6BT, UK; Andrew S Singleton: Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA.

Contributors SK drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. JLG drafting/revising the manuscript, study concept or design, analysis or interpretation of data. MAN drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. JK drafting/revising the manuscript and interpretation of data. RC revising the manuscript and analysis or interpretation of data. AB drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. JCC drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. GY drafting/revising the manuscript and interpretation of data. KC drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. PD drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. JSC drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. JLG drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. MAN, ABS, JMB, JH, JJ, PH were responsible for patient characterisation and sample collection of the Kid sample. CK and JH were responsible for patient characterisation and sample collection of the Paris sample. TG and IW were responsible for patient characterisation and sample collection of the Tübingen sample. MAN, ABS, JMB, JH, JJ, PH were responsible for patient characterisation and sample collection of the International Parkinson’s Disease Genomics Consortium. SK, JCC, AB, SL, MS, MM, FD, PP, PT, AD and MV were responsible for patient characterisation and sample collection of the French sample. PD, GC and CM were responsible for the 3C sample collection. FCB, KT assisted in experimental design and execution. All authors critically reviewed the manuscript.

Funding IPDGC: This US work was supported in part by the Intramural Research Programs of the National Institute on Aging, National Institute of Neurological Disorders and Stroke, National Institute of Environmental Health Sciences, National Human Genome Research Institute, National Institutes of Health, Department of Health and Human Services; project numbers Z01 AG000949-02 and Z01-E5101986. In addition this study was supported by the US Department of Defense, award number W81XWH-09-2-0128. Funding to support collection of a portion of the samples was obtained from the National Institutes of Health (grants NS057105 and RR024992), the American Parkinson Disease Association (APDA), Barnes Jewish Hospital Foundation and the Greater St Louis Chapter of the APDA. This work was supported in part by the Wellcome Trust/MRC Joint Call in Neurodegeneration award (WT089698B) to the UK Parkinson’s Disease Consortium (UKPDC) whose members are from the UCL/Institute of Neurology, the University of Sheffield, and the MRC Protein Phosphorylation Unit at the University of Dundee. Additionally part of the study was undertaken at UCL/UCL using funding through a Department of Health NIHR Biomedical Research Centre. This work was also supported by Parkinson’s UK (Grants 8047 and J-0804) and the Medical Research Council (G0700943). Genotyping of UK replication cases on ImuChip was done by the Wellcome Trust Case Control Consortium 2 project which is funded by the Wellcome Trust (085475/B/08/Z and 085475/Z/08/Z). PD was partly supported by a Wolfson-Royal Society Merit award. The UK gene expression work was supported in part by the UK Medical Research Council (G0901254) to researchers based in the UCL Institute of Neurology and King’s College London. JH receives support from the Reta Lila Weston Trust for Medical Research. This work was also supported by the Landschildt University Hospital Research Fund (5.Sv.), the Icelandic Research Council (5.Sv.), the European Community Framework Programme 7, People programme, iAPP on novel genetic and phenotypic markers of Parkinson’s disease and Essential Tremor (Mark MD), contract no PIAP-GA-2008-230596 MarkMD. (H Pettersson, J Holton). The KORA research platform (KORA): Cooperative Research in the Region of Augsburg: www.gsf.de/KORA) was initiated and financed by the Forschungszentrum für Umwelt und Gesundheit (GfSU), which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. The study was additionally funded by the German National Genome Network (NGFNplus #01G085134; German Ministry for Education and Research) and in addition by the German Federal Ministry of Education and Research (BMBF) NGFN (01G04R68) and in the frame of ERA-Net NEURON (01GW0908). This work was also supported by the Helmholtz Alliance Mental Health in an Ageing Society (HelMA, HA-215) funded by the Initiative and Networking Fund of the German Federal Ministry of Education and Research and by the State of Bavaria. The study was additionally funded by the National Genome Network (NGFNplus #01G085134; German Ministry for Education and Research) and in addition by the German Federal Ministry of Education and Research (BMBF) NGFN (01G04R68) and in the frame of ERA-Net NEURON (01GW0908). This work was also supported by the Helmholtz Alliance Mental Health in an Ageing Society (HelMA, HA-215) funded by the Initiative and Networking Fund of the German Federal Ministry of Education and Research (BMBF) NGFN (01G04R68) and in the frame of ERA-Net NEURON (01GW0908).
Medical genomics, the Prinses Beatrix Fonds (http://www.prinsesbeatrixfonds.nl) for sponsoring this work. This study utilised the high-performance computational capabilities of the Biowulf Linux cluster at the National Institutes of Health, Bethesda, Md. (http://biowulf.nih.gov). DNA panels and samples from the NINDS Human Genetic Resource Center DNA and Cell Line Repository (http://ccr.coriell.org/ ninds) were used in this study, as well as clinical data. The submitters that contributed samples are acknowledged in detailed descriptions of each panel (http://tcrr.coriell.org/sections/Collectons/NINDS/?sid=10). The authors thank The French Parkinson’s Disease Genetics Study Group: Y Agid, M Anheim, A-M Bonnet, M Borg, A Brice, E Broussolle, J-C Conov, Ph Damier, A Destee, A Dur, F Durif, S Durr, F E Lohmann, M Martinez, P Mollard, P Pollak, O Rascol, T Tranchant, M Véria, F Viallet and M Vidalen. The authors thank the members of the French 3C consortium: Drs Annick Alpérovitch, Claudine Berr, Christophe Tzourio and Jean-Charles Lambert for giving us the possibility to use part of the 3C cohort; and Drs M Lathrop and D Želenika for their support in generating the genome-wide molecular data. The UK brain samples for the gene expression studies were obtained from the MRC Sudden Death Brain Bank in Edinburgh. This study makes use of GWA data generated by the Wellcome Trust Case Control consortium 2 (WTCCC2) on UK PD cases and on UK controls from the 1958 Birth Cohort (SBBC) and National Blood Service (NBS). UK population control data was made available through WTCCC1. We thank Jeffrey Barrett for assistance with the design of the immunochip.

Competing interests None.

Ethics approval Local ethics committees.

Disclosure Dr Klebe received funding from the Deutsche Forschungsgemeinschaft (DFG) (DFG KI 1433/2-1). He received royalties from Thieme publishers. Dr Golmard reports no disclosures. Dr Nalls reports no disclosures. Dr Martinez reports no disclosures. Prof Singleton reports no disclosures. Dr Bras reports no disclosures. Prof. Hardy consults for Eisai Pharmaceuticals. Dr Javier Simon-Sanchez reports no disclosures. Dr Peter Heutink reports no disclosures. Dr Kuhlenbäumer received grants from the Deutsche Forschungsgemeinschaft (DFG), the regional government and the Christian-Albrechts-Universität Kiel. Prof Klein is supported by grants from the Hermann and Lilly Schilling Foundation and from the BMBF (01G02001), and the Bachmann-Strauss dystonia & Parkinson foundation. She also received consulting fees from Centogene and honoraria for speaking from Shire and Merz Pharma. Dr Charfri reports no disclosures. Dr Johann Hagenah receives funding Bachmann-Strauss dystonia & Parkinson foundation. Prof Gasser serves as an editorial board member of Parkinsonism and Related Disorders, Journal of Parkinson’s Disease and Neurogenetics and is funded by Novartis Pharma, the Federal Ministry of Education and Research (BMBF) (NGFN-Plus and ERA-Net NEURON), the Helmholtz Association (HelMA, Helmholtz Alliance for Health in an Ageing Society) and the European Community (MeCoPa, Mendelian Forms of Parkinsonism). He received speakers’ honoraria from Novartis, Merck-Serono, Schwarz Pharma, Boehringer Ingelheim and Valeant Pharma and royalties for his consulting activities from Cefalon Pharma and Merck-Serono. Prof. Gasser holds a patent concerning the LRRK2 gene and neurodegenerative disorders. I Wurster reports funding by GlaxoSmithKline for travel to a Congress. no disclosures. Dr Lesage reports no disclosures. Dr Lorenz reports no disclosures. Dr Deuschl has received lecture fees from Eisai, Lundbeck, Teva and Pollak and has been serving as a consultant for TEVA. He received royalties from Thieme publishers. He is a government employee and he receives through his institution funding for his research from the German Research Council, the German Ministry of Education and Health and Medtronic. Dr Saad reports no disclosures. Prof Durif reports no disclosures. Prof Pollak received speaker honoraria for Novartis and Medtronic. Prof Damier served on the European advisory board for Lundbeck–Teva and received honoraria for conferences given on behalf Novartis and GlaxoSmithKline. Prof Tison has received speaker honoraria from UCB, Novartis, Lundbeck, GSK, Boehringer Ingelheim and Aquestasant on a scientific advisory board for Novartis, Addex pharmaceuticals; received research grant from Novartis and received funding for travel from Novartis, UCB, Lundbeck. Dr Durr received honoraria from Pfizer Inc. for participating to the Global Tau Pathology Genetics Advisory Board, and received research support for the French Agency for Research. Dr Maubert is funded by the foundation “la recherche médicale” (FRM, France) and reports no disclosures. Dr Aoumess receives honoraria from a medical advisory board of Total and Ipsen, for lectures for Sanofi, Pfizer, Servier and holds stocks from Genescreen. Dr Lombert reports no disclosures. Dr Tzourio reports no disclosures. Dr Charbonnier-Beaupel reports no disclosures. Ms Tahiri reports no disclosures. Prof Vidalhét had institutional (ANR, BNP Paribas INGERS, and Patient’s association (France Parkinson) research grants. Prof. Brice received honoraria from the Wolfsion Foundation for reviewing scientific project, and received research support from the French Agency for Research, Programme Hospitalier de Recherche Clinique, European Community and patients associations. Dr Jean-Christophe Corvol received research grants from INSERM and APHP, and received speaker’s honoraria and travel reimbursements from Lundbeck, Biogen and Schering-Plough.

Provenance and peer review Not commissioned; externally peer reviewed.

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Stephan Klebe, Jean-Louis Golmard, Michael A Nalls, et al.

*J Neurol Neurosurg Psychiatry* 2013 84: 666-673 originally published online February 13, 2013
doi: 10.1136/jnnp-2012-304475

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