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RESEARCH PAPER

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

Stephan Klebe,^{1,2,3,4,5,6,7} Jean-Louis Golmard,⁸ Michael A Nalls,⁹ Mohamad Saad,^{10,11} Andrew B Singleton,⁹ Jose M Bras,¹² John Hardy,¹² Javier Simon-Sanchez,^{9,13} Peter Heutink,¹³ Gregor Kuhlenbäumer,¹⁴ Rim Charfi,^{15,16} Christine Klein,¹⁷ Johann Hagenah,¹⁷ Thomas Gasser,^{18,19} Isabel Wurster,^{18,19} Suzanne Lesage,^{1,2,3} Delia Lorenz,²⁰ Günther Deuschl,²⁰ Franck Durif,²¹ Pierre Pollak,²² Philippe Damier,²³ François Tison,²⁴ Alexandra Durr,^{1,2,3,4} Philippe Amouyel,^{25,26,27} Jean-Charles Lambert,^{25,26,27} Christophe Tzourio,^{28,29} Cécilia Maubaret,³⁰ Fanny Charbonnier-Beaupel,^{1,2,3} Khadija Tahiri,^{1,2,3} Marie Vidailhet,^{2,3,6,31} Maria Martinez,^{10,11} Alexis Brice,^{1,2,3,4,6} Jean-Christophe Corvol,^{1,2,3,5,15} French Parkinson's Disease Genetics Study Group and the International Parkinson's Disease Genomics Consortium (IPDGC)

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.

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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 trimodal 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 *COMT* 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.^{1–2} The substitution of valine (Val) by methionine (Met) at codon 158 (Val158Met) in the membrane-bound isoform, corresponding to codon 108 in the soluble form, results in a trimodal distribution of high, low and intermediate enzymatic activity. *COMT* activity is threefold to fourfold higher in the liver and red blood cells of 158Val patients than in those with the 158Met variant.^{3–4} There are ethnic differences in the distribution of the Val158Met genotype.⁵ 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).⁶

The influence of the *COMT* Val158Met polymorphism on non-motor symptoms in PD, particularly cognitive functions, has been studied^{7–11}

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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=1031) 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=2061) 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's disease (Idiopathic Parkinson Kohorte Syndroms, 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 χ^2 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 χ^2 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 V.9 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 Characteristics of subjects

	PD			Controls		
	n	Sex ratio	AAO	n	Sex ratio	Age at inclusion
All	5886	1.5	57.6±13.8	10723	1.01	60.0±10.1
US	937	1.5	57.8±13.2	3033	0.89	63.3±10.1
UK	1648	1.4	64.2±12.4	2699	1.07	53.0±0.0
NL	744	1.8	55.6±11.8	2019	0.79	55.7±5.8
France	1031	1.3	48.4±13.2	2061	1.20	73.0±6.4
Germany	1526	1.5	57.4±13.0	911	1.14	50.2±15.7

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

Movement disorders

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

	Total (% (n))	Control (% (n))	PD (% (n))	p Value
Val/Val	23.7 (3943)	23.6 (2526)	24.1 (1417)	0.22
Val/Met	49.5 (8214)	49.5 (5303)	49.5 (2911)	
Met/Met	26.8 (4452)	27.0 (2894)	26.5 (1558)	

Val/Val: homozygous for the Val158 allele; Val/Met: heterozygous; Met/Met: homozygous for the Met158 allele. p Value: multivariate analysis (see material and methods).
COMT, catechol-O-methyltransferase; PD, Parkinson's disease.

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 samples (56.2 ± 13.4 for Val/Val compared with 59.5 ± 12.7 for Met/Met, $p = 0.03$). For the UK, Dutch and German samples no significant changes could be found (data not shown).

The univariate analysis for the whole PD sample ($n = 5886$) found a significant difference of AAO according to genotype

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

	Met/Met	Val/Met	Val/Val	Univariate p value	Multivariate p value
Total	58.3 ± 13.5	57.4 ± 13.9	57.1 ± 13.9	0.041	0.026*
Men	57.9 ± 13.6	57.1 ± 13.6	56.0 ± 14.1	0.013	0.007**
Women	58.8 ± 13.3	57.7 ± 14.3	58.6 ± 13.4	0.29	0.81**

*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 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).

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 Val/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 controls 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 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.^{33–35} In postmortem studies, the dorsolateral prefrontal cortex of women had lower *COMT* activity than men.³⁶ Further evidence for gender differences comes from *COMT* knockout mice (*COMT*^{-/-}).³⁷ In this model dopamine levels in the frontal cortex are significantly increased in male *COMT*^{-/-} mice compared with wild-type mice, but not in female *COMT*^{-/-} mice. Sex hormones, especially oestrogen, probably contribute to explain gender differences. Oestrogens inhibit *COMT* mRNA expression in cells expressing oestrogen receptors.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,³⁹ despite steady oestradiol levels within this period.⁴⁰ Bearing this in mind further pathophysiological mechanism could be responsible for the sexual dimorphism like additional gene implication or epigenetic regulation.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 age⁴² and its activity is regulated by epigenetic factors.⁴³ Different SNPs of the *MAOB*⁴⁴ and the combination of genotypes at risk for the *MAOB* and the *COMT* gene⁴⁵ 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 *COMT**rs4680* (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 galactocerebrosidase gene mutation and the AAO has been suspected in PD.⁴⁶ Future studies must integrate the effects of environmental and genetic factors, including the *COMT* polymorphism, that could affect the bioavailability of dopamine in general, and especially in individuals at risk for PD.

In conclusion, our data indicate that the *COMT* polymorphism *rs4680* (Val158Met) is a genetic modifier of AAO in patients with PD, with a higher effect in male patients than in female patients. This may be important for future diagnostic and therapeutic strategies.

Author affiliations

¹INSERM, UMR_S975, CR-ICM, Paris, France

²UPMC University Paris 06, UMR_S975, CR-ICM, Pitié-Salpêtrière Hospital, Paris, France

³CNRS UMR 7225, CR-ICM, Pitié-Salpêtrière Hospital, Paris, France

⁴Assistance Publique Hôpitaux de Paris, Département de Génétique et Cytogénétique, Hôpital de la Pitié-Salpêtrière, Paris, France

⁵INSERM, CIC-9503, Hôpital de la Pitié-Salpêtrière, Paris, France

⁶Assistance Publique Hôpitaux de Paris, Department of Neurology, Hôpital de la Pitié-Salpêtrière, Paris, France

⁷Department of Neurology, University Hospital Würzburg, Würzburg, Germany

⁸Assistance Publique Hôpitaux de Paris, Department of Biostatistics, Hôpital de la Pitié-Salpêtrière, Paris, France

⁹Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda Maryland, USA

¹⁰INSERM U1043, CPTP, Toulouse, France

¹¹Paul Sabatier University, Toulouse, France

¹²Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK

¹³Department of Clinical Genetics Section of Medical Genomics, VU Medical Center, Amsterdam, Netherlands

¹⁴Institute of Experimental Medicine, Christian-Albrechts University, Kiel, Germany

¹⁵Assistance Publique Hôpitaux de Paris, Department of Pharmacology, Hôpital de la Pitié-Salpêtrière, Paris, France

¹⁶Faculté de Médecine de Tunis, Université de Tunis El Manar, Centre National de Pharmacovigilance de Tunis, Service de Pharmacologie Clinique, Tunis, Tunisia

¹⁷Institute of Neurogenetics, University of Lübeck, Lübeck, Germany

¹⁸Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany

¹⁹Department of Neurodegenerative Diseases, German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany

²⁰Department of Neurology, UKS-H, Campus Kiel; Christian-Albrechts-University, Kiel, Germany

²¹Hôpital Gabriel Montpied, CHU de Grenoble, Department of Neurology, Clermont-Ferrand, France

²²CHU de Grenoble, Department of Neurology, Grenoble, France

²³CHU de Nantes, Centre d'Investigation Clinique, Nantes, France

²⁴Hôpital Haut-Lévêque, Department of Neurology, Pessac, France

²⁵INSERM, U744, Lille, France

²⁶Institut Pasteur de Lille, Lille, France

²⁷Université Lille-Nord de France, Lille, France

²⁸Université Pierre et Marie Curie—Paris 6, CNRS 7225 CRICM, ER4-UPMC Modélisation en recherche clinique, Hôpital Pitié-Salpêtrière, Paris, France

²⁹INSERM UMR_S708, Neuroépidémiologie, Paris, France

³⁰INSERM U897, Université Bordeaux Ségalen, Bordeaux, France

³¹"Movement Disorders and Basal Ganglia: Pathophysiology and experimental Therapeutics", INSERM, UMR_S975, Paris, France

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Collaborators The French Parkinson's Disease Genetics Study Group includes, Y Agid: AP-HP, Hôpital de la Pitié-Salpêtrière, Department of Neurology, 75013 Paris, France; M Anheim: AP-HP, Hôpital de la Pitié-Salpêtrière, Département de Génétique et Cytogénétique, Centre de Génétique Moléculaire et Chromosomique, 75013 Paris, France; A-M Bonnet: AP-HP, Hôpital de la Pitié-Salpêtrière, Department of Neurology, 75013 Paris, France; M Borg: Service de Neurologie, Hôpital Pasteur, Nice, France; A. Brice: AP-HP, Hôpital de la Pitié-Salpêtrière, Department of Neurology, 75013 Paris, France; AP-HP, Hôpital de la Pitié-Salpêtrière, Département de Génétique et Cytogénétique, Centre de Génétique Moléculaire et Chromosomique, 75013 Paris, France; E Broussolle: University of Lyon; Hospices Civils de Lyon, Neurological Hospital, Lyon, France; J-C Corvol: INSERM, Centre d'Investigation Clinique CIC-9503, Hôpital de la Pitié-Salpêtrière, Paris, France; Ph. Damier: CHU Nantes, CIC0004, Department of Neurology, Nantes, France; +A. Destée: University Lille-Nord de France, CHRU de Lille, Neurologie, Hôpital Roger Salengro, Lille Cedex, France; A Durr: AP-HP, Hôpital de la Pitié-Salpêtrière, Département de Génétique et Cytogénétique, Centre de Génétique Moléculaire et Chromosomique, 75013 Paris, France; F Durif: Hôpital Gabriel Montpied, Department of Neurology, Clermont-Ferrand, France; S Klebe: AP-HP, Hôpital de la Pitié-Salpêtrière, Département de Génétique et Cytogénétique, Centre de Génétique Moléculaire et Chromosomique, 75013 Paris, France; E Lohmann: AP-HP, Hôpital de

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la Pitié-Salpêtrière, Département de Génétique et Cytogénétique, Centre de Génétique Moléculaire et Chromosomique, 75013 Paris, France; M Martinez: INSERM U563, CPTP, Toulouse, France; C Penet: INSERM, U975, 75013 Paris, France; P Pollak: CHU de Grenoble, Department of Neurology, Grenoble, France; P Krack: CHU de Grenoble, Department of Neurology, Grenoble, France; O Rascol: Departments of Clinical Pharmacology and Neurosciences, Hospital and University Paul Sabatier de Toulouse, France; F Tison: Hôpital Haut-Lévêque, Department of Neurology, Pessac, France; C Tranchant: Department of Neurology, Hôpital Civil, Strasbourg, France; M Vérin: Service de Neurologie, Hôpital Pontchaillou, CHU de Rennes, Rennes, France; F Viallet: Service de Neurologie, CHU La Timone, Marseille, France and M Vidailhet: AP-HP, Hôpital de la Pitié-Salpêtrière, Department of Neurology, 75013 Paris, France. International Parkinson's Disease Genomics Consortium (IPDGC) includes—Michael A Nalls: Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA; Vincent Plagnol: UCL Genetics Institute, Gower Place, London, WC1E 6BT, UK; Jose M Bras: Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG; Dena G Hernandez: Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA, Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG; Manu Sharma: INSERM UMR 1043, CPTP, Toulouse, France; Una-Marie Sheerin: Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG; Mohamad Saad: INSERM UMR 1043, CPTP, Toulouse, France, Paul Sabatier University, Toulouse, France; Javier Simón-Sánchez: Department of Clinical Genetics, Section of Medical Genomics, VU University Medical Centre, Amsterdam, The Netherlands; Claudia Schulte: Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany; Suzanne Lesage: INSERM, UMR_S975 (Formerly UMR_S679), Paris, France, Université Pierre et Marie Curie-Paris, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, UMR-S975, Paris, France, CNRS, UMR 7225, Paris, France; Sigurlaug Sveinbjörnsdóttir: Department of Neurology, Landspítali University Hospital, Reykjavik, Iceland, Department of Neurology, MEHT Broomfield Hospital, Chelmsford, Essex, UK, Queen Mary College, University of London, London, UK; Philippe Amouyel: ⁵¹INSERM U744, Lille, France, Institut Pasteur de Lille, Université de Lille Nord, Lille, France; Sampath Arepalli: Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA; Gavin Band: Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7LJ, UK; Roger A Barker: Department of Neurology, Addenbrooke's Hospital, University of Cambridge, Hills Road, Cambridge CB2 2QQ; Céline Bellinguez: Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7LJ, UK; Yoav Ben-Shlomo: Department of Social Medicine, Bristol University; Henk W Berendse: Department of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands; Daniela Berg: Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany; Kailash Bhatia: Department of Motor Neuroscience, UCL Institute of Neurology, Queen Square, London WC1N 3BG; Rob MA de Bie: Department of Neurology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Alessandro Biffi: Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA 02114, USA, Department of Neurology, Massachusetts General Hospital, Boston, MA 02114, USA, Program in Medical and Population Genetics, Broad Institute, 7 Cambridge Center, Cambridge, MA 02139, USA; Bas Bloem: Department of Neurology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Zoltan Bochdanovits: Department of Clinical Genetics, Section of Medical Genomics, VU University Medical Centre, Amsterdam, The Netherlands; Michael Bonin: Department of Medical Genetics, Institute of Human Genetics, University of Tübingen, Tübingen, Germany; Kathrin Brockmann: Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany; Janet Brooks: Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA; David J Burn: Newcastle University Clinical Ageing Research Unit, Campus for Ageing and Vitality Newcastle upon Tyne NE4 5PL UK; Gavin Charlesworth: Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG; Honglei Chen: Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, North Carolina, USA; Patrick F Chinnery: Neurology M4104, The Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH UK; Sean Chong: Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA; Carl E Clarke: School of Clinical and Experimental Medicine, University of Birmingham, Edgbaston, Birmingham B15 2TT, Department of Neurology, City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Dudley Road, Birmingham B18 7QH; Mark R Cookson: Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA; J Mark Cooper: Department of Clinical Neurosciences, UCL Institute of Neurology, Royal Free Campus, Rowland Hill Street, London NW3 2PF; Jean Christophe Corvol: INSERM, UMR_S975 (Formerly UMR_S679), Paris, France, Université Pierre et Marie Curie-Paris, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, UMR-S975, Paris, France, CNRS, UMR 7225, Paris, France, INSERM CIC-9503, Hôpital Pitié-Salpêtrière, Paris, France; Carl Counsell: University of Aberdeen, Division of Applied Health Sciences, Population Health Section, Polwarth building, Foresterhill, Aberdeen, AB25 2ZD; Philippe Damier: CHU Nantes, CIC0004, Service de Neurologie, Nantes, France; Jean-François Dartigues: INSERM U897, Université Victor Segalen, Bordeaux, France; Panos Deloukas: Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK; Günther Deuschl³⁷, ³⁷Klinik für Neurologie, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Christian-Albrechts-Universität Kiel, Kiel, Germany; David T Dexter: Parkinson's Disease Research Group, Faculty of Medicine, Imperial College London, 4th Floor, Burlington Danes Building, Hammersmith Hospital, Du Cane Road, W12 0NN London, UK; Karin D van Dijk: Department of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands; Allissa Dillman: Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA; Frank Durif: Service de Neurologie, Hôpital Gabriel Montpied, Clermont-Ferrand, France, Alexandra Dürr: INSERM, UMR_S975 (Formerly UMR_S679), Paris, France, Université Pierre et Marie Curie-Paris, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, UMR-S975, Paris, France, CNRS, UMR 7225, Paris, France, AP-HP, Pitié-Salpêtrière Hospital, Department of Genetics and Cytogenetics, Paris, France; Sarah Edkins: Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK; Jonathan R Evans: Cambridge Centre for Brain Repair, Forvie Site, Robinson Way, Cambridge CB22PY, UK; Thomas Foltynie: Institute of Neurology, University College London, London, UK; Colin Freeman: Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7LJ, UK; Jianjun Gao: Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, North Carolina, USA; Michelle Gardner: Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG; Raphael Gibbs: Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA, Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG; Alison Goate: Department of Psychiatry, Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, USA; Emma Gray: Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK; Rita Guerreiro: Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG; Ómar Gústafsson: deCODE genetics, Sturlugata 8, IS-101 Reykjavik, Iceland; Clare Harris: University of Aberdeen, Division of Applied Health Sciences, Population Health Section, Polwarth building, Foresterhill, Aberdeen, AB25 2ZD; Garrett Hellenthal: Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7LJ, UK; Jacobus J van Hilten: Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands; Albert Hofman: Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands; Albert Hollenbeck: AARP, Washington DC, USA; Janice Holton: Queen Square Brain Bank for Neurological Disorders, Institute of Neurology, University College London, London, UK; Michele Hu: Department of Clinical Neurology, West Wing, Level 3, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU; Xuemei Huang: Departments of Neurology, Radiology, Neurosurgery, Pharmacology, Kinesiology & Bioengineering, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, Pennsylvania; Heiko Huber: Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany; Gavin Hudson: Neurology M4104, The Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH UK; Sarah E Hunt: Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK; Johanna Huttenlocher: deCODE genetics, Sturlugata 8, IS-101 Reykjavik, Iceland; Thomas Illig: Institute of Epidemiology, Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, Germany; Pálmi V Jónsson: Department of Geriatrics, Landspítali University Hospital, Reykjavik, Iceland; Cordelia Langford: Cambridge Centre for Brain Repair, Forvie Site, Robinson Way, Cambridge CB22PY, UK; Andrew Lees: Queen Square Brain Bank for Neurological Disorders, Institute of Neurology, University College London, London, UK; Peter Lichtner: Institute of Human Genetics, Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, Germany; Patricia Limousin: Institute of Neurology, Sobell Department, Unit of Functional Neurosurgery, Queen Square, London, UK; Grisel Lopez: Section on Molecular Neurogenetics, Medical Genetics Branch, NHGRI, National Institutes of Health, Bethesda, Maryland, USA; Delia Lorenz: Klinik für Neurologie, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Christian-Albrechts-Universität Kiel, Kiel, Germany; Alisdair McNeill: Department of Clinical Neurosciences, UCL Institute of Neurology, Royal Free Campus, Rowland Hill Street, London NW3 2PF; Catriona Moorby: School of Clinical and Experimental Medicine, University of Birmingham, Edgbaston, Birmingham B15 2TT; Matthew Moore: Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA; Huw Morris: MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, CF14 4XN, UK; Karen E Morrison: School of Clinical and Experimental Medicine, University of Birmingham, Edgbaston, Birmingham B15 2TT, Neurosciences Department, Queen Elizabeth Hospital, University Hospitals

Birmingham NHS Foundation Trust, Birmingham B15 2TH; Ese Mudanohwo: Neurogenetics Unit, UCL Institute of Neurology/National Hospital for Neurology and Neurosurgery, Queen Square, London, UK; Sean S O'Sullivan: Queen Square Brain Bank for Neurological Disorders, Institute of Neurology, University College London, London, UK; Justin Pearson: MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, CF14 4XN, UK; Richard Pearson: Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7LJ, UK; Joel S Perlmutter: Department of Psychiatry, Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, USA; Hjörvar Pétursson: deCODE genetics, Sturlugata 8, IS-101 Reykjavik, Iceland, Department of Medical Genetics, Institute of Human Genetics, University of Tübingen, Tübingen, Germany; Matti Pirinen: Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7LJ, UK; Pierre Pollak: Service de Neurologie, CHU de Grenoble, Grenoble, France; Bart Post: Department of Neurology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Simon Potter: Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK; Bernard Ravina: Translational Neurology, Biogen Idec, 14 Cambridge Center, Bio 6, Cambridge, Massachusetts, USA; Tamas Revesz: Queen Square Brain Bank for Neurological Disorders, Institute of Neurology, University College London, London, UK; Olaf Riess: Department of Medical Genetics, Institute of Human Genetics, University of Tübingen, Tübingen, Germany; Fernando Rivadeneira: Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; Patrizia Rizzu: Department of Clinical Genetics, Section of Medical Genomics, VU University Medical Centre, Amsterdam, The Netherlands; Mina Ryten: Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG; Stephen Sawcer: University of Cambridge, Department of Clinical Neurosciences, Addenbrooke's hospital, Hills Road, Cambridge, CB2 0QQ, UK; Anthony Schapira: Department of Clinical Neurosciences, UCL Institute of Neurology, Royal Free Campus, Rowland Hill Street, London NW3 2PF; Hans 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, Medical Genetics Branch, NHGRI, National Institutes of Health, Bethesda, Maryland, USA; Rohan de Silva: Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG; Colin Smith: Department of Pathology, Wilkie Building, Teviot Place, Edinburgh, EH8 9AG; Chris CA Spencer: Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7LJ, UK; Hreinn Stefánsson: 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: Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7LJ, UK; Zhan Su: Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7LJ, UK; Kevin Talbot: University of Oxford, Department of Clinical Neurology, John Radcliffe Hospital, Oxford OX3 9DU; Charlie M Tanner: Clinical Research Department, The Parkinson's Institute and Clinical Center, Sunnyvale, California, USA; Avazeh Tashakkori-Ghanbaria: Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK; François Tison: Service de Neurologie, Hôpital Haut-Lévêque, Pessac, France; Daniah Trabzuni: Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG; Bryan J Traynor: Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA; André G Uitterlinden: Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; Jana Vandrovcova: Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG; Daan Velseboer: Department of Neurology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Marie Vidailhet: INSERM, UMR_S975 (Formerly UMR_S679), Paris, France, Université Pierre et Marie Curie-Paris, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, UMR-S975, Paris, France, CNRS, UMR 7225, Paris, France; Damjan Vukcevic: Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7LJ, UK; Robert Walker: Department of Pathology, Wilkie Building, Teviot Place, Edinburgh, EH8 9AG; Bart van de Warrenburg: Department of Neurology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Michael E Weale: King's College London, Department of Medical and Molecular Genetics, London SE1 9RT; Mirdhu Wickremaratchi: Department of Neurology, Cardiff University, Cardiff, UK; Nigel Williams: MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, CF14 4XN, UK; Caroline H Williams-Gray: Department of Neurology, Addenbrooke's Hospital, University of Cambridge, Hills Road, Cambridge CB2 2QQ; Sophie Winder-Rhodes: Department of Psychiatry and Medical Research Council/Wellcome Trust Behavioural and Clinical Neurosciences Institute, University of Cambridge, Cambridge, UK; Kári Stefánsson, deCODE genetics, Sturlugata 8, IS-101 Reykjavik, Iceland; Maria Martinez: INSERM UMR 1043, CPTP, Toulouse, France, Paul Sabatier University, Toulouse, France; Peter Donnelly: Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3

7LJ, UK; John Hardy: Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG; Peter Heutink: Department of Clinical Genetics, Section of Medical Genomics, VU University Medical Centre, Amsterdam, The Netherlands; Alexis Brice: INSERM, UMR_S975 (Formerly UMR_S679), Paris, France, Université Pierre et Marie Curie-Paris, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, UMR-S975, Paris, France, CNRS, UMR 7225, Paris, France, AP-HP, Pitié-Salpêtrière Hospital, Department of Genetics and Cytogenetics, Paris, France; Thomas Gasser: Department of Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany; Nicholas W Wood: UCL Genetics Institute, Gower Place, London, WC1E 6BT, UK, Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, WC1N 3BG; Andrew B 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. GK 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. GK, DL and GD were responsible for patient characterisation and sample collection of the Kiel sample. CK and JH were responsible for patient characterisation and sample collection of the Lübeck sample. TG and IW were responsible for patient characterisation and sample collection of the Tübingen sample. MAN, ABS, JMB, JHy, JSS, 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, PD, FT, AD and MV were responsible for patient characterisation and sample collection of the French sample. PA, JCL, CT and CM were responsible for the 3C sample collection. FCB, KT assisted in experimental design and execution. All authors critically reviewed the manuscript.

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

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