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Report

Identification of a Novel *LRRK2* Mutation Linked to Autosomal Dominant Parkinsonism: Evidence of a Common Founder across European Populations

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Autosomal dominant parkinsonism has been attributed to pathogenic amino acid substitutions in leucine-rich repeat kinase 2 (LRRK2). By sequencing multiplex families consistent with a *PARK8* assignment, we identified a novel heterozygous *LRRK2* mutation. A referral sample of 248 affected probands from families with autosomal dominant parkinsonism was subsequently assessed; 7 (2.8%) were found to carry a heterozygous *LRRK2* 6055G→A transition (G2019S). These seven patients originate from the United States, Norway, Ireland, and Poland. In samples of patients with idiopathic Parkinson disease (PD) from the same populations, further screening identified six more patients with *LRRK2* G2019S; no mutations were found in matched control individuals. Subsequently, 42 family members of the 13 probands were examined; 22 have an *LRRK2* G2019S substitution, 7 with a diagnosis of PD. Of note, all patients share an ancestral haplotype indicative of a common founder, and, within families, *LRRK2* G2019S segregates with disease (multipoint LOD score 2.41). Penetrance is age dependent, increasing from 17% at age 50 years to 85% at age 70 years. In summary, our study demonstrates that *LRRK2* G2019S accounts for parkinsonism in several families within Europe and North America. Our work highlights the fact that a proportion of clinically typical, late-onset PD cases have a genetic basis.

Parkinsonism is a clinical syndrome characterized by bradykinesia, resting tremor, muscle rigidity, and postural instability (Gelb et al. 1999). Parkinson disease (PD [(MIM 168600]) is the second most frequent neurodegenerative disorder, after Alzheimer disease; it affects >1% of the population aged >55 years and is the most common cause of parkinsonism (de Rijk et al. 1995). Neuropathological findings in PD are loss of pigmented neurons in the brain stem—substantia nigra and locus coeruleus—with intracellular Lewy body inclusions found within surviving neurons (Forno 1996).

Although PD is considered a sporadic disease, various hereditary forms of parkinsonism have been recognized (Vila and Przedborski 2004). A major breakthrough in recent years has been the mapping and cloning of a number of genes causing monogenic forms of parkinsonism. The role of genetics in sporadic late-onset PD has, however, remained controversial due, in part, to the different associated pathologies and the variable but overlapping spectrum of clinical signs and symptoms seen in monogenic familial forms of parkinsonism.

Genomic multiplication and missense mutations in the

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Table 1

Novel Chromosome 12 STR Markers

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α-synuclein gene were initially identified in a small number of families with autosomal dominant parkinsonism (*PARK1* [MIM 168601] and *PARK4* [MIM 605543]) (Polymeropoulos et al. 1997; Kruger et al. 1998; Singleton et al. 2003; Chartier-Harlin et al. 2004; Farrer et al. 2004; Zarranz et al. 2004). Patients present with levodopa-responsive parkinsonism, although early-onset dementia is frequent (Spira et al. 2001). α-Synuclein antibodies robustly stain Lewy bodies and Lewy neurites in familial and sporadic PD (Spillantini et al. 1997), and common genetic variability in the *α-synuclein* promoter has been implicated in sporadic PD (Pals et al. 2004).

Autosomal recessive mutations in three genes—*parkin, DJ-1,* and *PINK1*—have been linked with early-onset (i.e., subjects aged <45 years at onset) parkinsonism (*PARK2* [MIM 600116 and MIM 602544], *PARK6* [MIM 605909], and *PARK7* [MIM 606324]) (Kitada et al. 1998; Bonifati et al. 2003; Valente et al. 2004*a*). A large number of pathogenic mutations and rearrangements have been identified in the *parkin* gene (reviewed by Mata et al. [2004]). Mutations in the *DJ-1* and *PINK1* genes seem to be more rare (Abou-Sleiman et al. 2003; Valente et al. 2004*b*).

Our group recently identified pathogenic mutations in a novel gene, the leucine-rich repeat kinase 2 gene (*LRRK2*), in six families with autosomal dominant parkinsonism linked to the *PARK8* locus (MIM 607060) (Zimprich et al. 2004*a*). Paisan-Ruiz and colleagues (2004) independently confirmed these findings in British and Basque families. The *PARK8* locus was originally mapped in a large Japanese family, the Sagamihara family, presenting with autosomal dominant parkinsonism (Funayama et al. 2002). Across *PARK8*-linked families, the age at onset of symptoms is late (aged >50 years), albeit variable. Brain autopsy findings in four members of the Sagamihara family showed pure nigral neuronal degeneration without coexisting pathology (Funayama et al. 2002). In contrast, nigral neuronal loss, tauopathy, and Lewy body synucleinopathy have been described elsewhere for families A and D (Wszolek et al. 2004; Zimprich et al. 2004*a*).

Here, we describe a novel *LRRK2* mutation in 13 families from diverse North American and European origins. Segregation analysis provided evidence of pathogenicity and an estimate of age-associated penetrance, whereas haplotype analysis suggested that the mutation originates from a common and ancient founder.

Patients and control individuals in this study were examined by neurologists specialized in movement disorders. A full history, including family history and neurological examination, was completed for each patient. A clinical diagnosis of PD required the presence of at least two of three cardinal signs (resting tremor, bradykinesia, and rigidity), improvement through adequate dopaminergic therapy, and the absence of atypical features or other causes of parkinsonism. Families with two or more members affected by PD in at least two consecutive generations were considered to be consistent with an autosomal dominant pattern of inheritance. The institutional review boards of all participating institutions approved our clinicogenetic protocols, and informed consent was obtained from all patients and control subjects.

Blood samples were taken and genomic DNA was extracted using standard techniques. Six small families (194, 281, 3081, 3082, 3083, and 3211) were identified elsewhere with positive LOD scores (range 0.29–0.38) for microsatellite markers within the *PARK8* locus (Zimprich et al. 2004*b*). For each of these probands, all 51 exons of the *LRRK2* gene were amplified by PCR and were sequenced. Electrophoresis was performed under standard conditions on an ABI 3730 automated sequencer, and data were analyzed with SeqScape software version 2.1.1 (Applied Biosystems) and were compared with the published sequence of *LRRK2* (GenBank accession number AY792511). Primers are available on request.

On identification of a novel, heterozygous *LRRK2* 6055G→A transition (G2019S) in the proband and affected sibling of family 3211, we designed a probe employing TaqMan chemistry on ABI 7900 (Applied Biosystems) to screen for this specific mutation. We examined another 242 affected probands with familial parkinsonism that was consistent with autosomal dominant transmission of disease. These probands and their families were referred from many regions of North America, Asia, and Europe. Positive samples originated from centers in the United States, Norway, Ireland, and Poland. Hence, we subsequently assessed whether *LRRK2* 6055G→A (G2019S) was common in appropriate population samples. We screened 435 Norwegian, 271 Irish, and 100 Polish patients with idiopathic PD and 1,200 American, 550 Norwegian, 330 Irish, and 180 Polish control subjects (2,260 control individuals in total). All mutations discovered were confirmed by direct sequencing. Finally, all participating family members of *LRRK2* G2019S–substitution carriers (affected and unaffected) were screened for the mutation.

In available family members, 17 microsatellite markers and four SNPs were genotyped for linkage analyses and to determine whether a single haplotype was associated with the *LRRK2* mutation. Microsatellite markers were chosen to span the *PARK8* region, including *D12S87, D12S1648, D12S2080, D12S2194,*

Table 2

Allele Frequencies of *PARK8* Markers

The table is available in its entirety in the online edition of *The American Journal of Human Genetics*.

D12S1048, D12S1301, and *D12S1701*. *LRRK2* is located between *D12S2194* and *D12S1048*. We also developed 10 novel microsatellite markers in this region (table 1) by searching for repeat polymorphisms by use of the RepeatMasker software (RepeatMasker Web site) with *in silico* BAC sequences covering the *PARK8* locus (University of California–Santa Cruz Genome Bioinformatics). (The physical position of markers is from the National Center for Biotechnology Information [NCBI] build 34.) One primer of each pair was labeled with a fluorescent tag. PCR reactions were performed under standard conditions, and PCR products were run on an ABI 3100 genetic analyzer. Results were analyzed using Genescan 3.7 and Genotyper 3.7 software (Applied Biosystems). The four exonic *LRRK2* SNPs included were *rs7966550, rs1427263, rs11176013,* and *rs11564148*. Marker-allele frequencies were estimated by genotyping unrelated individuals from North America (table 2).

Multipoint LOD scores for all families were calculated under the assumption of an autosomal dominant model by use of GENEHUNTER-PLUS (Kong and Cox 1997). The frequency of the deleterious allele was set at 0.0001; marker-allele frequencies were determined empirically. The map positions for each marker were taken from Rutgers combined linkage physical map, version 1.0 (MAP-O-MAT Web site). For tightly linked loci with no observed recombinants, intermarker genetic distances were assigned as 0.01 cM. *PARK8* haplotypes were established for families with known phase; for those affected individuals or families for whom chromosomal phase could not be determined, both alleles are given (fig. 1). Haplotype frequencies in the general population were estimated from unrelated individuals by use of an estimation-maximization algorithm (Zaykin et al. 2002).

Age-dependent penetrance was estimated as the probability of a gene carrier becoming affected, at a given age, within the 13 families. The number of affected mutation carriers within each 5-year age group was divided by the total number of carriers (both affected and unaffected) within that group. For some affected family members, no DNA was available, and only historical data on the disease course was obtained. Those individuals were excluded from penetrance calculations.

We identified a heterozygous 6055G→A mutation in 7 (2.8%) of 248 probands from families presenting with autosomal dominant parkinsonism. Subsequently, six additional patients carrying the same mutation were identified through population-based screening in samples of European descent. In total, we identified 13 families: 7 originate from Norway, 3 from the United States, 2 from

	Family												
Marker	**P-063**	**P-089**	**P-104**	**P-241**	**P-369**	**P-394**	**F05**	**1210**	**1120**	**111**	**3211**	**PD66**	**1P**
D12S87	160	160	164	164	-	156	166	156/158	164	160	158	156/166	156/158
D12S1648	120	120	122	122	122	110	110	122/124	110	110	110	120/134	128/130
D12S2080	188	188	188	188	188	188	188	184/192	188	180	184	188/192	184/188
D12S2194	265	265	265	265	265	265	261	253/261	257	257	253	245/249	249/261
D12S2514	291	291	291	291	291	291	291	291	291	291	291	291/294	285/291
D12S2515	224	224	224	224	224	224	224	220/224	224	224	224	216	212/220
rs7966550	T	T	T	T	T	T	T	T	T	T	T	T	T
D12S2516	254	254	254	254	254	254	254	254	254	254	254	254	254
rs1427263	A	A	A	A	A	A	A	A	A	A	A	A	A
rs11176013	G	G	G	G	G	G	G	G	G	G	A/G	G	A/G
rs11564148	A	A	A	A	A	A	T/A	T/A	A	A	T/A	A	T/A
D12S2518	154	154	154	154	154	154	154	154	154	154	154	154	154
D12S2519	132	132	132	132	132	132	132	132	132	132	132/138	132/138	132/134
D12S2520	260	260	260	260	257/260	260	260	257/260	260	257/260	260	248/260	254/260
D12S2521	359	359	327/359	359	359	359	359	359/367	359	359	359	323/363	359/379
D12S2522	297	297	297	297	297	297	297	297	297	297	295/297	281/297	297
D12S2523	320	320	320	320	320	320	320	320	320	320	314/320	317/320	305/320
D12S2517	190	190	190	190	190	190	190	190/194	194	194	192	184/190	184/188
D12S1048	214	214	214	214	214	211/214	214	214/223	214	214	223	211/214	211/226
D12S1301	112	116	120	120	116	116	116	108/116	100	120	116	100/116	100
D12S1701	95	97	91	91	95	95/97	97	95/101	92	91/95	95	97/101	91/97
	Norway							**United States**			**Ireland**		**Poland**
	Country of origin												

Figure 1 Chromosome 12q12 markers on the disease haplotype (*PARK8*). Genotypes for mutation carriers from 13 families with *LRRK2* G2019S are shown; those shared are highlighted in gray. For families whose phase could not be determined with certainty, both alleles are shown.

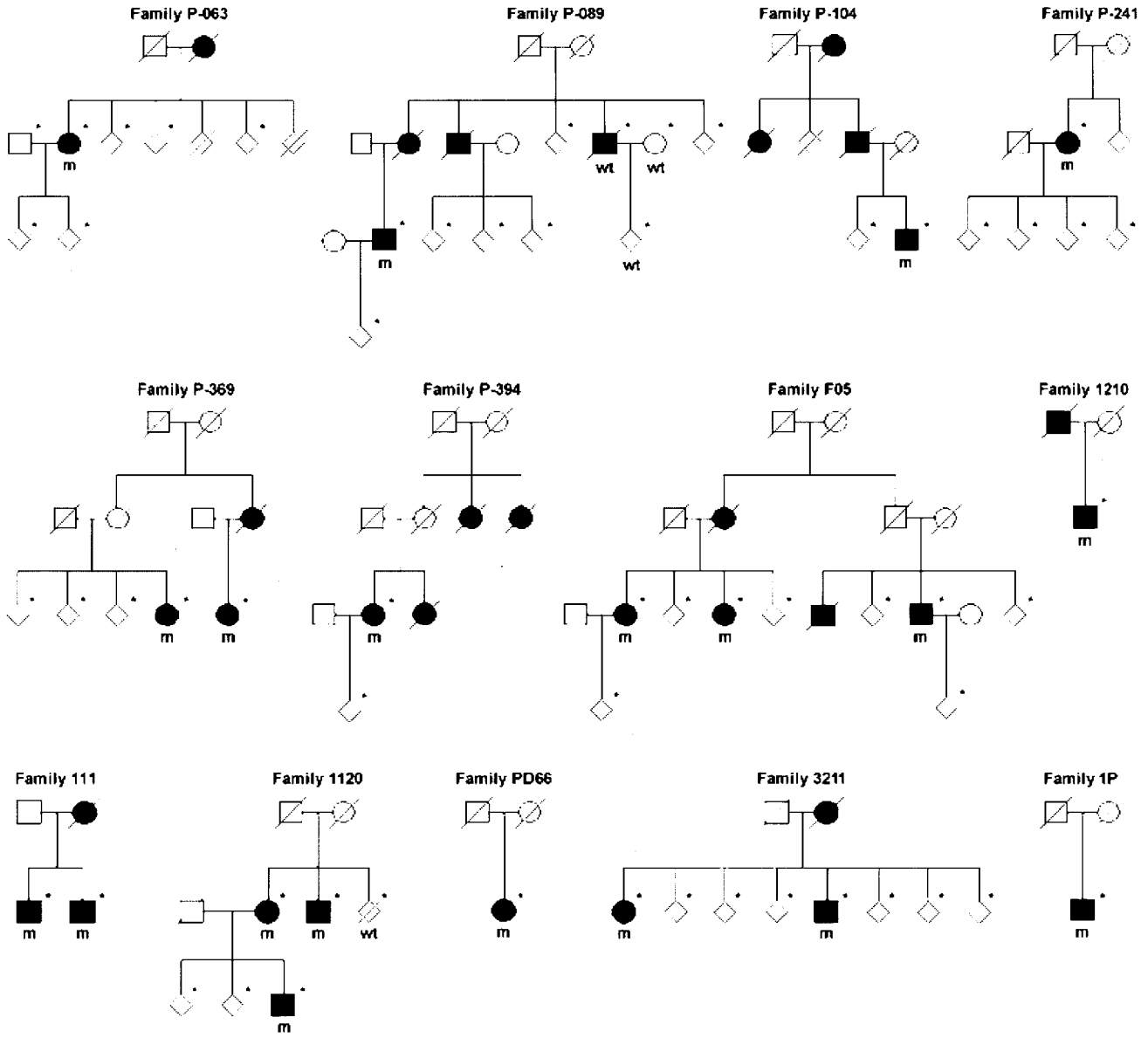

Figure 2 Pedigrees of families with *LRRK2* G2019S. Blackened symbols denote family members affected with parkinsonism. An asterisk (*) denotes a genotyped individual, with "m" for mutation carriers and "wt" for wild-type *LRRK2*. To protect confidentiality, the genotypes and sexes of some unaffected individuals are not shown, and some family members for whom no information was available have been removed from the pedigrees.

Ireland, and 1 from Poland. Of the U.S. families, one was reported to be of Russian/Romanian ancestry (family 1120), a second claimed to be of Italian descent (family 1210), and the ethnic origin was unknown for a third kindred (family 111). After genotyping 42 additional family members, 22 were found to carry the mutation, 7 with a diagnosis of PD (table 3).

Three of the six original patients identified through the population-based screening had no known family history of PD. In the 10 remaining kindreds, the *LRRK2* G2019S substitution segregates with disease, consistent with autosomal dominant transmission with reduced, age-associated penetrance. Simplified versions of the family pedigrees are presented in figure 2. Of note, a recently deceased member of family P-089 was affected but was not an *LRRK2* mutation carrier. He had akinetic rigid parkinsonism unresponsive to levodopa. Although his chromosome 12q12 haplotypes were consistent with

Table 3

Demographic and Clinical Information for 13 Families with *LRRK2* G2019S

Characteristic	Findings for Family												
	P-063	P-089	P-104	P-241	P-369	P-394	F05	1210	111	1120	PD66	3211	1P
Country of origin	Norway	Norway	Norway	Norway	Norway	Norway	Norway	United States	United States	United States	Ireland	Ireland	Poland
No. of generations	3	4	3	3	3	4	4	2	2	3	1	2	1
No. of affected individuals	2	4	4	1	3	4	5	2	3	3	1	3	1
No. of typed individuals affected (unaffected)	1 (6)	2 (8)	1 (1)	1 (4)	2 (3)	1 (1)	3 (6)	1 (0)	2(0)	3 (3)	1 (0)	2 (6)	1 (0)
No. of typed generations	2	3	1	2	1	2	2	1	1	2	1	1	1
Age[a] at onset in years (range)	59 (53–65)	59 (43–70)	58	60	50 (43–61)	66	64 (61–70)	65	58 (57–58)	59 (39–78)	41	46 (40–52)	73
Maximum mLOD score	0	.30	0	0	.60	0	.90	0	.09	.30	0	.30	0

[a] Average ages at onset are given when $n \geq 2$ affected individuals.

The figure is available in its entirety in the online edition of *The American Journal of Human Genetics*.

Figure 3 Penetrance of *LRRK2*-associated disease, showing the probability of becoming affected by parkinsonism, in *LRRK2* G2019S carriers, as a function of age.

those of his offspring and siblings, he did not carry the disease-associated *PARK8* haplotype. Hence, for the purposes of this study, he was considered a phenocopy and was excluded from further analyses. We did not identify the mutation in any of 2,260 control individuals.

Evidence for linkage to the *PARK8* locus was found across families, with a combined maximum multipoint LOD (mLOD) score of 2.41, corresponding to a P value of 4.3×10^{-4}. Positive LOD scores were found in all families in which more than one affected subject was genotyped (table 3). Since only a defined chromosomal region was investigated, rather than a genomewide search being done, the mLOD score exceeds that required for significance, $P = .01$ (Lander and Kruglyak 1995).

All affected members from the different families, except the phenocopy in family P-089, share a chromosome 12q12 and *LRRK2* haplotype (fig. 1). Phase can be established for most markers in nine of the families; *LRRK2* 6055G→A mutation carriers share alleles for eight adjacent markers, including four exonic SNPs and four microsatellites. For the remaining families, the number of available samples from relatives was not sufficient to determine phase. However, the genotypes in these cases are consistent with a common *LRRK2* G2019S allele. *D12S2516* is located in intron 30, and *D12S2518* is located in intron 45, whereas the two other shared markers are positioned 3′ of the *LRRK2* gene. SNP *rs7966550* is located in exon 22, and the remaining three SNPs are in exon 34. With use of the physical position of the shared and nonshared markers, the size of the shared haplotype was determined to be between 145 kb and 154 kb. The frequency of this haplotype is estimated to be 6.0% in the U.S. population (not considering the frequency of the *LRRK2* 6055G→A mutation).

Age at onset of clinical symptoms was variable, even within the same family. Family 1120 had both the earliest and latest age at onset for a patient. The youngest affected patient had onset at age 39 years, whereas the oldest carrier presented with initial symptoms at age 78 years. Where recorded, most *LRRK2* G2019S carriers have late-onset disease (aged >50 years at onset). The mean age at onset for affected mutation carriers ($n = 19$) was 56.8 years (range 39–78 years). Unaffected carriers ($n = 15$) have a mean age of 54.6 years (range 26–74 years). The penetrance of the mutation was found to be highly age dependent, increasing from 17% at age 50 years to 85% at age 70 years (fig. 3).

We have identified a novel 6055G→A (G2019S) *LRRK2* mutation in 13 white kindreds originating from several European and North American populations. In 10 families, the mutation segregates with autosomal dominant parkinsonism; three probands had no family

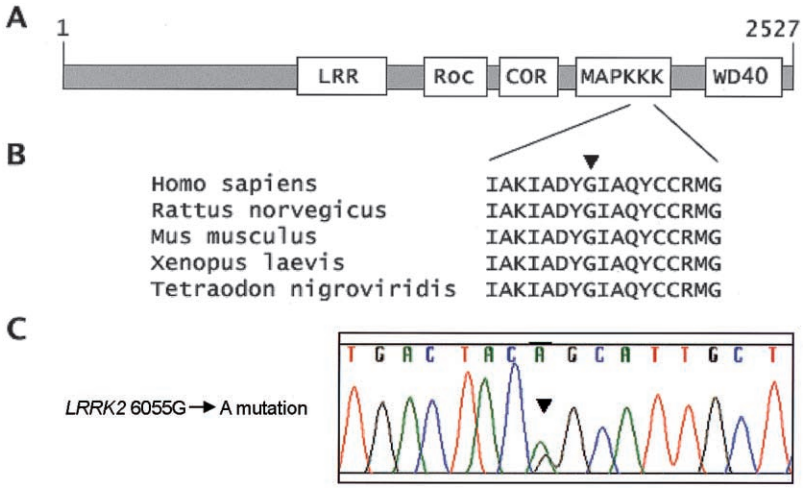

Figure 4 *LRRK2* with the novel G2019S substitution. *A,* Schematic drawing of *LRRK2* with predicted protein domains. LRR = leucine-rich repeat; Roc = Ras in complex proteins; COR = C-terminal domain of Roc; MAPKKK = mitogen-activated protein kinase kinase kinase; WD40 = WD40 repeats. *B,* The human LRRK2 protein sequence in the region of the G2019S mutation, aligned with orthologs from rat (GenBank accession number XP_235581), mouse (GenBank accession number AAH34074), frog (GenBank accession number AAH76853), and puffer fish (GenBank accession number CAG05593). The mutation is indicated by a blackened arrowhead. *C,* Chromatogram showing the 6055G→A transition (G2019S).

The figure is available in its entirety in the online edition of *The American Journal of Human Genetics*.

Figure 5 Aligned amino acid sequences of the activation segment of different human kinases.

history of PD. Positive mLOD scores were obtained in multiplex families and, combined, provide significant support for the *PARK8* locus. The *LRRK2* G2019S substitution was absent in a large number of control individuals of similar ethnicity. The physical size of the shared haplotype is small, between 145 kb and 154 kb. *LRRK2* is located close to the centromere on chromosome 12, and there is generally a dearth of recombination at centromeres. *LRRK2* spans several haplotype blocks, but local patterns of linkage disequilibrium are not available for the specific populations we have studied (International HapMap Project). The mutant allele is geographically widespread across European and American populations and is therefore likely to be ancient. The number of families linked to *LRRK2* in this and previous studies now explains a proportion of genetically defined autosomal dominant parkinsonism greater than that explained by other genes.

Age is the single most consistent risk factor for development of PD and other neurodegenerative disorders (Lang and Lozano 1998), and our data also indicate that age is an important risk factor in *LRRK2*-associated parkinsonism. The mean age at onset, 56.8 years, of patients with the *LRRK2* 6055G→A mutation in this study is comparable to that of patients in other families linked to *PARK8* (Funayama et al. 2002; Paisan-Ruiz et al. 2004; Zimprich et al. 2004*a*). The majority of patients in all families present with late-onset disease that is difficult to clinically distinguish from typical idiopathic PD. We found that the penetrance of of *LRRK2* G2019S–associated disease was highly age dependent, increasing in a close-to-linear fashion from 17% at age 50 years to 85% at age 70 years. Interestingly, age at onset was variable in this study, both within and between different families, which suggests that other susceptibility factors, environmental or genetic, may influence the phenotype.

Although our findings clearly indicate that *LRRK2* mutations account for a proportion of familial late-onset parkinsonism, historically, cross-sectional twin studies have not supported a genetic etiology for late-onset PD (Tanner et al. 1999; Wirdefeldt et al. 2004). The age-associated penetrance of *LRRK2* mutations provides some explanation, since even large and well-designed twin studies are underpowered to detect incompletely penetrant mutations (Simon et al. 2002). *LRRK2* mutations were also found in patients with apparently sporadic PD; three of the patients in the present study did not have any known affected first- or second-degree relatives. However, a caveat for the study of age-dependent penetrance is that carriers may die of other diseases before manifesting or being diagnosed with PD. Thus, it seems difficult to separate sporadic and familial PD and to hypothesize environmental causes as more important in one group and genetic causes as more prominent in the other. In light of these results, a family history of parkinsonism, previously considered an exclusion criterion for a diagnosis of PD, must be reconsidered (Hughes et al. 1992).

LRRK2 is a member of the recently defined ROCO protein family (Bosgraaf and Van Haastert 2003). In human, mouse, and rat, members of the ROCO protein family have five conserved domains (fig. 4). The LRRK2 kinase domain belongs to the MAPKKK subfamily of kinases. The active sites of all kinases are located in a cleft between an N-terminal and a C-terminal lobe, typically covered by an "activation segment," in an inactive conformation. The activation segment must undergo crucial structural changes to allow access to peptide substrates and to orient key catalytic amino acids (Huse and Kuriyan 2002). In different kinases, the activation segment starts and ends with the conserved residues asp-phe-gly (DFG) and ala-pro-glu (APE), respectively (Nolen et al. 2004). The *LRRK2* G2019S substitution changes the highly conserved glycine (G) at the start of this segment (fig. 5). In a German family we described elsewhere, an I2020T mutation is located in an adjacent codon (Zimprich et al. 2004*a*). In other kinases, oncogenic mutations in residues within the activation segment of the kinase domain have an activating effect (Davies et al. 2002). Thus, we postulate that *LRRK2* G2019S and I2020T mutations may have an activating effect on the kinase activity of *LRRK2*. A mutation causing "gain of function" of the resulting protein would also be compatible with the dominant mode of disease transmission observed in the presented families.

The identification of *LRRK2* mutations as a cause of parkinsonism in a large number of families from different populations heralds an exciting time in the field of neurogenetics. The elucidation of the functional effects of this gene and of the G2019S substitution will further our understanding of pathways that play a pivotal role in PD.

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Electronic-Database Information

The accession number and URLs for data presented herein are as follows:

GenBank, http://www.ncbi.nih.gov/Genbank/ (for *LRRK2* [accession number AY792511], rat [accession number XP_235581], mouse [accession number AAH34074], frog [accession number AAH76853], and puffer fish [accession number CAG05593])
International HapMap Project, http://www.hapmap.org/
MAP-O-MAT, http://compgen.rutgers.edu/mapomat/ (for version 1.1)
NCBI, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=nucleotide
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *PARK1, PARK4, PARK2, PARK6, PARK7,* and *PARK8*)
RepeatMasker, http://www.repeatmasker.org/
University of California–Santa Cruz Genome Bioinformatics, http://genome.ucsc.edu/

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