Influence of Heterozygosity for Parkin Mutation on Onset Age in Familial Parkinson Disease

The GenePD Study

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Background: The PARK2 gene at 6q26 encodes parkin, whose inactivation is implicated in an early-onset autosomal recessive form of Parkinson disease (PD).

Objective: To evaluate the influence of heterozygosity for parkin mutation on onset age in a sample of families with at least 2 PD-affected members.

Design: Clinical and genetic study.

Setting: Twenty collaborative clinical sites.

Patients: Patients with familial PD collected in the GenePD study. Studied families were selected for (1) affected sibling pairs sharing 2 alleles identical by state at PARK2 (D6S305) or (2) 1 or more family members with onset age younger than 54 years, regardless of D6S305 status. At least 1 member from each of 183 families underwent comprehensive screening for deletion/insertion variants and point mutations in PARK2.

Main Outcome Measures: Mutations in the parkin gene were screened by means of single-stranded conformation polymorphism and sequencing in all 12 coding exons and flanking intronic sequences for point mutations and duplex quantitative polymerase chain reaction in all exons for rearrangement, duplication, and deletion.

Results: Mutations were found in 23 families (12.6% of those screened). Among the mutation-positive families, 10 (43%) contained compound heterozygotes; 3 (13%), homozygotes; and 10 (43%), heterozygotes. The onset age in patients with parkin gene mutations ranged from 20 to 76 years. Patients with 1 parkin mutation had an 11.7-year age at onset than did patients with none (P = .04), and patients with 2 or more parkin mutations had a 13.2-year decrease in age at onset compared with patients with 1 mutation (P = .04).

Conclusions: These data indicate that parkin mutations are not rare in multiply affected sibships, and that heterozygous mutation carrier status in PARK2 significantly influences age at onset of PD.

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Parkinson disease (PD) (Mendelian Inheritance in Man 168600) is the second most common neurodegenerative disorder, with a prevalence of approximately 1% among persons 60 years or older, increasing to 4% or 5% among persons 85 years or older.1 Parkinson disease is characterized by a progressive loss of dopaminergic neurons in the substantia nigra. Although most cases of PD occur as a sporadic disease of unknown etiology, a positive family history is one of the strongest known risk factors for PD.2 Genes for 5 rare monogenic forms of PD have been identified. Point mutations or dosage increase of the α-synuclein gene and mutations in the recently identified gene encoding leucine-rich repeat kinase 2 (LRRK2) cause autosomal dominant parkinsonism, whereas mutations in the genes for parkin, DJ-1, and phosphatase and tensin homologue (PTEN)–induced putative kinase 1 (PINK1) cause autosomal recessive forms of parkinsonism.3-9

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with autosomal recessive inheritance. The frequency and spectrum of parkin mutations have been extensively studied in large, ethnically mixed patient populations by several PD study groups. The frequency of parkin mutations was estimated to be as much as 50% in autosomal recessive juvenile parkinsonism, 10% to 25% in early-onset PD, and 2% to 6% in late-onset PD. However, the reported mutation rate varied by PD sample tested and the detection methods used. Furthermore, it is not clear whether heterozygosity for parkin influences PD risk or onset age.

In this study, we evaluated the burden of parkin mutations in 183 families selected from a total of 329 families with at least 2 PD-affected members collected in the GenePD Study.

**METHODS**

**PATIENTS AND FAMILIES**

Data from sibling pairs affected with PD and their families, if available, were collected at 20 clinical sites throughout North America, Europe, and Australia as part of the collaborative GenePD Study. Neurologists from the participating sites examined and confirmed the PD diagnosis for each individual, according to the United Kingdom PD Society Brain Bank Criteria, with minor modification described previously. All neurologists participated in interrater reliability training to ensure diagnostic consistency. All participants granted and signed informed consent.

**GENOTYPING**

Genomic DNA was extracted from lymphocytes through the use of a DNA extraction kit (Nucleon II; Amersham Pharmacia Biotech, Piscataway, NJ). The microsatellite marker D6S305 (AFM242g5, with heterozygosity of 0.84; Center for Medical Genetics, Marshfield, Wis), which lies in intron 7 of the parkin gene, was genotyped. Thirty nanograms of genomic DNA was amplified by means of polymerase chain reaction (PCR) using the marker’s primer set in a 10-µL reaction, incorporating α-32P-deoxyguanosine triphosphate. The samples were denatured and resolved on a gel formulation (0.5X SequaGel MD; National Diagnostics, Atlanta, Ga) at a constant 6 W for 12 to 16 hours at room temperature, according to the standard protocol. The gel was dried and exposed to autoradiography using a standard technique. Those samples showing a band shift were further sequenced by the Massachusetts General Hospital DNA sequencing core using a DNA analyzer (ABI377XL or ABI3730; Applied Biosystems Inc, Foster City, Calif). Forward and reverse primers were used with sequencing chemistry (BigDye Terminator v3.1 kit; Applied Biosystems Inc), according to the manufacturer’s protocol. Novel sequence changes were investigated in 50 control subjects, by means of restriction fragment length polymorphism analysis when possible or by means of single-stranded conformation polymorphism analysis.

Gene dosage analysis was performed by quantitative duplex PCR of all 12 exons of PARK2 on a commercially available system (LightCycler; Roche Diagnostics, Mannheim, Germany) using the fluorescence resonance energy transfer technique. The β-globin gene was coamplified with each individual parkin exon and served as an internal standard. Primers, probes, and details of the method were as previously published. The standard curves were generated using human genomic DNA (Roche Diagnostics) in concentrations of 5, 1.25, and 0.3125 ng/µL. Sample concentrations were inferred on the basis of regression curves of the standards. Concentrations outside the range of the standard templates were disregarded and adjusted. All samples were measured in duplicate, and the results were accepted only within a range of less than 10% of the standard deviation of the 2 inferred sample concentrations. Coamplification of the β-globin gene provided a relative ratio of the parkin–β-globin gene concentration. A ratio of 0.8 to 1.2 was considered normal, 0.4 to 0.6 designated a heterozygous deletion, 1.3 to 1.7 indicated a heterozygous duplication, and 1.8 to 2.2 was considered a homozygous duplication or a triplication. All detected gene dosage variations were confirmed at least twice. A normal DNA sample was measured in parallel for each run to serve as a control.

For parkin exon 1 and 12 duplications, we also tested our mutation-positive samples by means of multiplex ligation-dependent probe amplification (MLPA) using the kit protocol provided by the manufacturer (MRC-Holland, Amsterdam, the Netherlands; http://www.mrc-holland.com). The sequences and preparation of the probes were according to protocol, as follows. One pair of probes in exon 1, 2 pairs of probes in exon 12 in the parkin gene, and 2 pairs of autosomal control probes were selected and synthesized; each was hybridized to a unique target sequence of unique size. For each sample, 50 to 100 ng of genomic DNA in 5 µL of buffer consisting of 10mM Tris (pH, 8.0) and 0.1mM EDTA (TE buffer; Boston BioProducts, Inc, Worcester, Mass) was denatured for 5 minutes at 98°C, after which 3 µL of the probe mix was added. The mixture was heated at 95°C for 1 minute and incubated at 60°C for 16 to 18 hours. Ligation was performed by adding 32 µL of ligation mix containing the temperature-stable ligase-65 enzyme (MRC-Holland) for 15 minutes at 54°C. Then the ligation was inactivated by incubation for 5 minutes at 98°C. For PCR amplification, 10 µL of ligated probes was mixed with 30 µL of PCR buffer and incubated in a PCR machine at 60°C, and a 10-µL mix was added containing deoxyribonucleotide triphos-

**MUTATIONAL ANALYSIS**

To detect point mutations and small deletions/insertions, we performed single-stranded conformation polymorphism analysis after amplification of all 12 exons of the parkin gene, using published intronic primers. Thirty nanograms of genomic DNA was amplified by means of PCR using the primer set of each exon in a 10-µL reaction, incorporating α-32P-deoxyguanosine triphosphate. The samples were denatured and resolved on a gel formulation (0.5X SequaGel MD; National Diagnostics, Atlanta, Ga) at a constant 6 W for 12 to 16 hours at room temperature, according to the standard protocol. The gel was dried and exposed to autoradiography using a standard technique. Those samples showing a band shift were further sequenced by the Massachusetts General Hospital DNA sequencing core using a DNA analyzer (ABI377XL or ABI3730; Applied Biosystems Inc, Foster City, Calif). Forward and reverse primers were used with sequencing chemistry (BigDye Terminator v3.1 kit; Applied Biosystems Inc), according to the manufacturer’s protocol. Novel sequence changes were investigated in 50 control subjects, by means of restriction fragment length polymorphism analysis when possible or by means of single-stranded conformation polymorphism analysis.
phates, Taq polymerase, and universal 3’-N-(3-fluoranthyl) maleimide-labeled primer (GGGTCTCCCTAAGGGTTGGA) and the 3’ primer (TCTAGATTGGATCTTGCTGGCAC). The PCR was carried out for 30 to 32 cycles (30 seconds at 95°C, 30 seconds at 60°C, and 1 minute at 72°C). The fragments were analyzed on a capillary sequencer (ABI model 3730 XL; Applied Biosystems Inc) using the manufacturer’s size standards (Genescan-ROX 500; Applied Biosystems Inc). Fragment analysis was performed using commercially available software (GeneMapper, version 3.7; Applied Biosystems Inc). Data were exported by spreadsheet (Excel; Microsoft Corp, Redmond, Wash).

To determine the relative quantity of the amplified probes in each sample, the relative peak areas for each probe were calculated as fractions of the total sum of peak areas in the sample. The average peak fractions of the corresponding probe in all samples were distributed around 3 distinct means. The patients carrying 0, 1, and 2 or more mutations had onset 13.2 years earlier than patients with 1 mutation (P=.04) (Figure 2 and Table 2). At least 1 parkin mutation was found in 23 of the 183 index patients, corresponding to 12.6% of the index sample screened. Among the mutation-positive families, 10 (43%) contained compound heterozygotes, 3 (13%) contained homozygotes, and 10 (43%) contained heterozygotes. Two families (families 1 and 8) each carried 3 putative mutations (Table 1). In family 1, 3 known mutations were found in both affected siblings. In exon 12, c.1289G>A (p.Gly430Asp) and c.1310C>T (p.Pro437Leu) resided on different chromosomes; in exon 3, c.337_376del was observed. In family 8, the index patient was found to have a homozygous exon 1 duplication, or a triplication, and an exon 12 duplication; however, the affected sibling did not carry any of these mutations, suggesting that PD of multiple etiologies may occur within the same family. We identified 7 previously described point mutations/small deletions and 2 novel alterations in 14 families that included 25 subjects (Figure 1). The 2 novel variants were a heterozygous missense mutation (p.Arg402His) and a heterozygous silent mutation (p.Leu307Leu), which were each detected in only 1 family. The changes segregated with the disease in the family and were not detected in 364 unrelated PD and 100 control chromosomes. We also detected 9 gene dosage alterations in 15 families that included 28 patients (Figure 1). Duplications of exons 1 and 12 in the parkin gene have not been previously reported. Surprisingly, exon 1 duplication was relatively common and was detected in 4 families in our sample set, whereas exon 12 duplication was detected in a single family. These changes were not detected in 252 control chromosomes, indicating that they are not merely polymorphisms.

The mean±SD onset age of patients with any parkin mutation was 42.9±14.1 years (38 mutation-positive patients with onset age data), and the oldest observed age at onset was 76 years. We used generalized estimating equation models to test the effect of the number of parkin mutations on onset age in the 91 families with affected siblings sharing both alleles IBS at the PARK2 locus. We used only this subset of families for testing because they were selected for parkin screening independent of their onset ages. We observed that the onset ages of the subjects carrying 0, 1, and 2 or 3 mutations were distributed around 3 distinct means. The patients with 1 parkin mutation had PD onset 11.7 years earlier than patients with no mutation (P=.04); and patients with 2 or more parkin mutations had onset 13.2 years earlier than patients with 1 mutation (P=.04) (Figure 2 and Table 2).

Parkin was initially identified as the product of a gene responsible for autosomal recessive juvenile parkinsonism characterized by an onset before age 20 years. Parkin mutations have since been found in older-onset forms of PD and in PD families with varied clinical and pathological phenotypes, including families with pseudodominant inheritance. The range of onset ages in patients with the parkin mutation has been expanded, from juvenile and early onset to after age 70 years. This indicates a wide involvement of parkin in PD; therefore, mutation screening should be considered for large-scale...
Table 1. Parkin Mutations Identified in This Study*

<table>
<thead>
<tr>
<th>Family</th>
<th>No. of Affected Members</th>
<th>Onset Age, y</th>
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<th>AA Change</th>
<th>Mutation 2</th>
<th>AA Change</th>
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Abbreviations: AA, amino acid; Het, heterozygous; Hom, homozygous; NA, not available; ellipses, none.

*Newly identified mutations are in boldface type. Nucleotides are numbered according to GenBank NM_004562 (parkin, human) with the A of the initiator ATG numbered as 1.
†Indicates 3 mutations found in this family.
‡Indicates no mutation found.
§Indicates affected parent.

Figure 1. Schematic representation of distribution of parkin mutations identified in this study. The diagram shows the 12 exons (Ex) that compose the coding sequences in the parkin gene. The ubiquitinlike domain, in-between RING (really interesting new gene), and RING-finger motifs in the predicted protein are marked. The point mutations are indicated above the sequence, and the exon rearrangements are shown below the sequence. For mutations identified in more than 1 family, the number of families with the mutation is given in parentheses. Newly identified mutations are in boldface type. The identified mutations are distributed across the entire gene. UTR indicates untranslated region.

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Figure 2. Distribution of onset age in patients having 0, 1, and 2 or more mutations in the PARK2 gene for Parkinson disease, selected by alleles identical by state. Patients with 1 PARK2 mutation had a 11.7-year younger onset than patients with no mutation (P=.04); and patients with 2 or more PARK2 mutations had nearly a 13.2-year decrease in onset age compared with patients with 1 mutation (P=.04).
quantitative duplex PCR to detect exon deletions and duplications, by altered gene dosage. We found a total of 23 families (12.6%) carrying at least 1 variant in the parkin gene.

We identified 18 different mutations, including 9 point mutations/small deletions and 9 insertion/deletion alterations. To our knowledge, 4 mutations are described for the first time in this study, including 2 exon rearrangements (exons 1 and 12 duplications) and 2 point mutations. Exon 1 duplication was detected in 4 families in our sample. To verify whether the duplication was a spurious multiplication of exons caused by assay artifact, we subjected these mutation-positive samples to retesting using the semiquantitative MLPA assay. The duplication in exon 1 was consistently identified by both assays in these 4 index patients and was not detected among 126 control subjects. The confirmation of the duplication by both assays supports the validity of this mutation in parkin. These results further suggest that exon 1 duplications have been underestimated in past studies because the high GC content of this exon makes these duplications difficult to detect. Exon 12 duplication was found in a single index patient and was not seen in 126 control subjects. Two single base pair substitutions, c.919C>A and c.1205G>C, were also detected. The latter alters a highly conserved acidic amino acid, whereas the former could conceivably alter splicing or regulation of the messenger RNA. Neither change was detected in 364 unrelated PD and 100 control chromosomes, suggesting that they are likely to be pathogenic, although it cannot be excluded that they are rare polymorphisms. Two other reports have recently described different variants affecting the latter amino acid position, p.Arg402Cys and p.Arg402Trp. These 2 variants were also found in 1 of 500 and 1 of 192 control chromosomes, respectively, and therefore it remains unclear whether these variants represent rare polymorphisms or pathogenic mutations.

Although parkin mutations were presumed recessive, there is increasing evidence suggesting that heterozygous mutations may confer increased susceptibility to late-onset PD. However, without testing exon rearrangements, the study by Oliveira et al may have missed mutations, thereby inflating the rate of heterozygosity. In the present study, a heterozygous mutation was found in 10 (43.5%) of 23 mutation-positive families. The heterozygous mutations we found have been reported previously as pathogenic in patients with single or compound heterozygous mutations. Although several studies have observed that patients with 1 mutation have a later onset than those with 2 mutations, few studies have compared their onset ages with those of patients without parkin mutations.

To test whether a single parkin mutation influences onset age in PD, we compared the onset age in the subgroup of patients selected for sharing 2 alleles IBS at PARK2. We found that patients with 0, 1, or 2 or more mutations in the parkin gene fell into 3 clusters. Patients with 0 or 2 or more mutations had the youngest mean onset age, patients with 1 mutation had an intermediate mean onset age, and patients with no mutations had the oldest mean onset age. These data strongly support the idea that carriers of heterozygous parkin mutation have a younger onset age compared with individuals with no parkin mutations. Although we cannot rule out the possibility that the heterozygous mutation is unrelated to disease or that a second mutation was not detected owing to technical limitations, the observation that the distribution of onset ages for carriers of heterozygous parkin mutations is not bimodal and is positioned between the other 2 samples supports the notion that a single parkin mutation influences onset age in PD. Recently, reports of neuroimaging data, including positron emission tomography and transcranial ultrasonography findings, showed preclinical changes in carriers of heterozygous parkin mutation, providing further support for our conclusion.

In conclusion, parkin mutations are not rare in this selected subset of familial PD samples (12.6%). Homozygous and compound heterozygous parkin gene mutations are associated with early-onset PD (mean onset age, 36 years). Single parkin mutations may increase susceptibility to the disease and decrease the onset age of PD (mean onset age, 49.6 years). Identification and removal of subjects with parkin gene mutations from subsequent genome-wide analyses will reduce the genetic heterogeneity in the sample, thereby increasing the power to detect linkage to other chromosomal regions contributing to the susceptibility to PD and/or influencing onset age.

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REFERENCES


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