Systematic Review and UK-Based Study of PARK2 (parkin), PINK1, PARK7 (DJ-1) and LRRK2 in Early-Onset Parkinson’s Disease

Laura L. Kilarski, PhD,1 Justin P. Pearson, MRCP,1 Victoria Newsway, BSc,1 Elisa Majounie, PhD,1 M. Duleek W. Knipe, BSc, MPH,2 Anjum Misbahuddin, PhD MRCP,3 Patrick F. Chinnery, PhD, FRCP.4 David J. Burn, MD, FRCP,4 Carl E. Clarke, MD, FRCP,5,6 Marie-Helene Marion, MD,7 Alistair J. Lewthwaite, MRCP,5,8,9 David J. Nicholl, PhD, FRCP,5,6,10 Nicholas W. Wood, PhD, FRCP,11 Karen E. Morrison, DPhil, FRCP,5,8 Caroline H. Williams-Gray, PhD, MRCP,11 Jonathan R. Evans, PhD, MRCP,11 Stephen J. Sawcer, PhD FRCP,11 Roger A. Barker, PhD, MRCP,11 Mirdhu M. Wickremaratchi, PhD, MRCP,12 Yoav Ben-Shlomo, PhD, FFPH,13 Nigel M. Williams, PhD,1 and Huw R. Morris, PhD, FRCP1*

1MRC Centre for Neuropsychiatric Genetics and Genomics, Department of Neurology, School of Medicine, Cardiff University, Cardiff, United Kingdom
2Department of Neurology, School of Medicine, Cardiff University, Cardiff, United Kingdom
3Institute of Genetic Medicine, Newcastle University, Central Parkway, Newcastle upon Tyne, United Kingdom
4School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom
5Sandwell and West Birmingham Hospitals NHS Trust, United Kingdom
6Department of Neurology, St George’s Hospital, London, United Kingdom
7University Hospitals Birmingham NHS Trust, Birmingham, United Kingdom
8Department of Molecular Neuroscience, Institute of Neurology, University College London, London, United Kingdom
9City Hospital, Birmingham, United Kingdom
10Department of Clinical Neurosciences, University of Cambridge, Addenbrooke’s Hospital, Hills Road, Cambridge, United Kingdom
11Department of Neurology, Worthing Hospital, Worthing, United Kingdom
12School of Social and Community Medicine, Bristol University, Bristol, United Kingdom

ABSTRACT: Approximately 3.6% of patients with Parkinson’s disease develop symptoms before age 45. Early-onset Parkinson’s disease (EOPD) patients have a higher familial recurrence risk than late-onset patients, and 3 main recessive EOPD genes have been described. We aimed to establish the prevalence of mutations in these genes in a UK cohort and in previous studies. We screened 136 EOPD probands from a high-ascertainment regional and community-based prevalence study for pathogenic mutations in PARK2 (parkin), PINK1, PARK7 (DJ-1), and exon 41 of LRRK2. We also carried out a systematic review, calculating the proportion of cases with pathogenic mutations in previously reported studies. We identified 5 patients with pathogenic PARK2, 1 patient with PINK1, and 1 with LRRK2 mutations. The rate of mutations overall was 5.1%. Mutations were more common in patients with age at onset (AAO) < 40 (9.5%), an affected first-degree relative (8.9%), an affected sibling (28.6%), or parental consanguinity (50%). In our study EOPD mutation carriers were more likely to present with rigidity and dystonia, and 6 of 7 mutation carriers had lower limb symptoms at onset. Our systematic review included information from >5800 unique cases. Overall, the weighted mean proportion of cases with PARK2 (parkin), PINK1, and PARK7 (DJ-1) mutations was 8.6%, 3.7%, and 0.4%, respectively. PINK1 mutations were more common in Asian subjects. The overall frequency of mutations in known EOPD genes was lower than previously estimated. Our study shows an increased likelihood of mutations in patients with lower AAO, family history, or parental consanguinity. © 2012 Movement Disorder Society

Key Words: systematic review; PARK2; PINK1; PARK7; LRRK2; early-onset Parkinson’s disease; parkin, DJ-1

Additional Supporting Information may be found in the online version of this article.
*Correspondence to: Dr. Huw R. Morris, Neurology (C4), University Hospital of Wales, Cardiff CF14 4XN, United Kingdom; morrishr@cf.ac.uk

Funding agencies: This work was supported by the Medical Research Council UK (G0700943), Parkinson’s UK (Grant 8047), the Cambridge NIHR Biomedical Research Centre, the Midlands Neuroscience Teaching and Research Fund, the Sandwell and West Birmingham Hospitals NHS Trust, the Ipsen Fund, the Wellcome Trust, and a Patrick Berthoud Clinical Research Fellowship and Raymond and Beverly Sackler studentship.

Relevant conflicts of interest/financial disclosures: Nothing to report.

Full financial disclosures and author roles may be found in the online version of this article.

Received: 27 October 2011; Revised: 26 June 2012; Accepted: 12 July 2012
Published online 6 September 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.25132
Although Parkinson’s disease (PD) is generally considered a disorder of the elderly, it also affects a substantial number of younger individuals. The age-standardized prevalence rate for PD in the United Kingdom is around 140 per 100,000 population, and about 3.6% of PD patients develop symptoms before age 45, which is usually defined as early-onset PD (EOPD). Previous studies have indicated an increased familial recurrence risk in PD, and in EOPD in particular there is an increased risk in siblings compared with to parents, consistent with autosomal recessive disease.

There are 3 autosomal recessive genes for EOPD: PARK2 (NM_004562.2), coding for E3 ubiquitin-protein ligase parkin; PINK1 (NM_032409.2, PARK6), which codes for a serine/threonine protein kinase (PTEN-induced putative kinase 1); and PARK7 (NM_001123377.1), coding for DJ-1. Mutations in PARK2 and PINK1 are the most common causes of EOPD. However, reported mutation frequencies vary widely across studies, which may relate to differences in case ascertainment, ethnicity, and proportions of familial and/or consanguineous cases. Lücking and colleagues reported that up to 50% of familial and 18% of sporadic EOPD cases had pathogenic PARK2 mutations, whereas more recent studies have reported a pathogenic mutation frequency as low as 1.6%. Frequency estimates for PINK1 mutations tend to fall within a similarly broad range, whereas PARK7 mutations are generally very rare.

Mutations in LRRK2 (NM_198578.3), coding for leucine-rich repeat serine/threonine-protein kinase 2 (dardarin), are the most frequent cause of genetic PD, with the most common mutation (G2019S) accounting for 1% of sporadic and 4% of familial cases. The penetrance of LRRK2 mutations is age dependent—less than 20% at age 45 and more than 80% at age 80.

We aimed to estimate the prevalence of PARK2, PINK1, PARK7, and LRRK2 mutations in EOPD in a UK-based study. In addition, we aimed to provide an estimate of the proportion of EOPD patients with autosomal recessive mutations in a systematic review of previously published studies.

**Patients and Methods**

**UK Cohort Mutation Analysis**

EOPD was defined on the basis of the Queen Square Brain Bank criteria for the definition of PD (not including the presence of family history as an exclusion criterion) and age at onset (AAO) < 45 years. Unrelated cases were ascertained from an intensive community-based prevalence study in the city of Cardiff, South Wales, United Kingdom, and from referrals from neurologists and PD specialists in Wales and from the whole of the United Kingdom. There were 3 nested EOPD groups: Cardiff, Wales, and the United Kingdom. The Cardiff series was ascertained via a primary care PD survey, the Welsh group was ascertained through frequent contact with PD specialists in Wales, and the UK cases were primarily recruited from the British National Surveillance Unit and collaborating genetics centers. Pathogenic mutation frequency data will be most accurate in actively recruited sample series, as these series will be less susceptible to referral bias. Clinical data were collated on ethnicity, consanguinity, AAO, family history, and presenting symptoms where available. Cases were defined as familial if they had at least 1 affected first-degree relative.

The cohort was screened for mutations in PARK2, PINK1, PARK7, and LRRK2 exon 41. All exons in PARK2, PINK1, and PARK7 and in exon 41 of LRRK2 including approximately 40 bp of flanking intronic sequence were sequenced (Supplementary Table S1a–d). Fragments were amplified and sequenced using a BigDye Terminator Cycle Sequencing kit (Perkin Elmer Applied Biosystems, Cheshire, UK) and analyzed on an ABI3100 sequencer (Applied Biosystems, Foster City, CA). Sequence variants were compared with known mutations and variants documented in the MDPD and PDGene databases.

Exon copy number for all exons of PARK2 and PINK1, as well as exons 1, 3, 5, 6, and 7 of PARK7 was determined using the multiplex ligation-dependent probe amplification method (MLPA) with the SALSA P051 Parkinson’s probe mix kit (MRC-Holland, Amsterdam, the Netherlands) according to the manufacturer’s instructions. Sequences were analyzed using Lasergene SeqMan Pro v8.02 software (DNASTAR, Inc., Madison, WI). Statistical analysis comparing cases with and without mutations was performed using Fisher’s exact test and the Student t test as appropriate (STATA).

The study was approved by the Research Ethics Committee for Wales (studies 04/9/025, 05/9/058, and 09/09/35).

**Systematic Review**

For the systematic review we included all studies published from 2000 to March 2011 that had investigated the occurrence of pathogenic PARK2, PINK1, and/or PARK7 mutations in a given patient cohort using standard diagnostic criteria and provided information about family history, proband status, consanguinity, ethnicity, and type of mutations found. Studies not satisfying strict inclusion criteria (see supplementary data) were excluded from analysis. The
TABLE 1. Summary of pathogenic mutations in PARK2, PINK1, and LRRK2 found in 136 EOPD cases

<table>
<thead>
<tr>
<th>Cohort (n)</th>
<th>PARK2</th>
<th>PINK1</th>
<th>LRRK2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Homozygous</td>
<td>Compound heterozygous</td>
<td>Homozygous</td>
</tr>
<tr>
<td>Cardiff (14)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wales (82)</td>
<td>0</td>
<td>3 (3.7%)</td>
<td>0</td>
</tr>
<tr>
<td>UK (136)*</td>
<td>0</td>
<td>5 (3.7%)</td>
<td>1 (0.7%)</td>
</tr>
</tbody>
</table>

*The United Kingdom (UK) includes England and Wales.

A proportion of EOPD cases (AAO < 50) with 2 patho-
genic mutations in PARK2, PINK1, and/or PARK7 was calculated for each study and collectively. In about half the studies, family history was defined as positive if probands had at least 1 affected first-degree relative (usually restricted to siblings), but in about 15% of studies, family history was extended to second- and third-degree relatives, and no definition was provided in about 30% of studies. For the purposes of this study, all cases with any positive family history were classified as familial. Consanguinity was defined by pedigree information or patient self-reports; articles were included in the familial and consanguineous subanalyses if the prevalence of familial and consanguinity was reported in both mutation-negative and -positive patients. In some studies, cases had been pre-screened for mutations (usually in PARK2), and if published results were available, this was taken into account.

Study proportions and confidence intervals were calculated using Wilson’s technique. Weighted mean proportions and confidence intervals for different patient subgroups were calculated using a negative binomial regression model in order to model between-study heterogeneity (overdispersion) as in a random-effects model. Risk ratios (including 95% confidence intervals and P values) comparing prespecified subgroups were also calculated using this model. When calculating pooled proportions for different subgroups, studies with fewer than 2 patients in a given subgroup were excluded from analysis. All statistical calculations were made using STATA.

Results

UK Cohort Mutation Analysis

We ascertained 136 unrelated EOPD cases (56% male), resident in the UK. Fourteen cases were identified from the Cardiff community-based study and 68 from the regional ascertainment in Wales (see Supplementary Table S2). The mean AAO was 37 years (median, 39 years; interquartile range, 35–42 years). Most cases were white (97.8%) and sporadic (78.5%). We identified 1 homozygous mutation, 5 compound heterozygous mutations, and 1 pathogenic heterozygous mutation in our cohort, corresponding to an overall mutation rate of 5.1% (95% confidence interval [95% CI], 1.4%–8.9%) for all 4 genes combined (Table 1). No cases were identified in the Cardiff cohort, and mutation frequencies in the Wales and UK cohorts were comparable (Table 1). Clinical descriptions of these 7 cases with pathogenic mutations are available in the supplementary material. One PARK2 compound heterozygous mutation and 1 PINK1 homoz-
igenous mutation were found in a total of 29 familial cases (6.9%; 95% CI, 1.9%–21.9%). In comparison, only 3.8% (95% CI, 1.5%–9.2%) of sporadic cases had pathogenic PARK2 mutations, and none had pathogenic PINK1 mutations (Tables 1 and 2). Pathogenic mutations were detected in 1 of 2 consanguineous patients. No mutations or gene dosage changes were found in PARK7, and no cases with digenic mutations were identified.

Sequence analysis and gene dosage assessment of PARK2 revealed 5 compound heterozygous mutations in 4 sporadic cases and 1 familial case. In exon 5 of PINK1, we identified a homozygous point mutation in a consanguineous familial case of Filipino descent (L347P); see Tables 1 and 2. One white patient with sporadic decease from the tertiary-referral cohort was found to be heterozygous for the G2019S mutation in exon 41 of LRRK2.

In cases with AAO < 30 years (n = 14), the rate of mutations was 28.6%; in cases with AAO between 30 and 40 years (n = 61), the rate of mutations was 4.9%, and no mutations were found in cases with an AAO between 40 and 45 years (n = 61). Cases with pathogenic mutations had a lower mean AAO (25.5 vs 38.1 years; P = .02). About a third of cases (28.6%) with pathogenic mutations had an affected sibling, whereas the number of affected siblings for cases without pathogenic mutations was much lower (3.9%; P = 4.0 × 10⁻⁴). Furthermore, 14.3% of cases with pathogenic mutations were from a consanguineous family compared with 0.8% of cases without mutations (P = .1). Cases with pathogenic mutations were more likely to report rigidity or dystonia at

---

Movement Disorders, Vol. 27, No. 12, 2012

1524
presentation (71.4% vs 28.4%, \( P = .03 \)) but had a similar incidence of tremor (28.6% vs 36.3%, \( P = 0.5 \)). It is also notable that 6 of the 7 mutation-positive cases had onset in the lower limbs (Table 2).

**Systematic Review**

The initial literature search identified 1228 studies, of which 63 including our own met inclusion criteria, encompassing 5877 unique cases. The depth of clinical and demographic data provided varied between studies. The weighted mean AAO was 39.2 years, with a maximum AAO of 40–50 years, depending on the study. About one third of cases (27.2%) were familial, and 3.9% were consanguineous. Most patients studied (52.9%) were white, with Asian and Latin American patients making up 17.4% and 5.7% of cases, respectively; 24.0% of cases were either of undisclosed or of other ethnicities, for example, Arabic, black African, or Caribbean. Only about one third of the 63 studies (31.7%) included 100 or more cases.

Forty-three studies assessed the prevalence of \( \text{PARK2} \) (parkin) mutations in a total of 3952 patients, in whom the pooled proportion of mutation-positive cases was 8.6% (95% CI, 6.0%–12.4%; Fig. 1, Table S3). Of the \( \text{PARK2} \) mutations reported in completely described studies, 44.1% (95% CI, 34.4%–56.4%) were homozygous, and 55.9% (95% CI, 44.9%–69.7%) were compound heterozygous (Table S8a). Familial cases were more likely than sporadic cases to have mutations in \( \text{PARK2} \), with a proportion of 15.5% (95% CI, 10.3%–23.4%) versus 4.3% (95% CI, 2.7%–6.8%). The risk ratio for familial to sporadic cases was highly significant at 3.6 (95% CI, 2.0–6.7; \( P < 1.0 \times 10^{-4} \)). Only a small number of studies provided comprehensive information on consanguinity; however, in those inbred cases reported, the frequency of pathogenic mutations was much higher (31.4%; 95% CI, 18.5%–53.2%; Table S4) than in cases who were demonstrably outbred (7.7%; 95% CI, 5.0%–11.7%), and the risk ratio was highly significant at 4.3 (95% CI, 1.7–10.6; \( P = 2.0 \times 10^{-3} \)). Pathogenic \( \text{PARK2} \) mutation frequencies among white and Asian cases were similar at 7.7% (95% CI, 4.6%–13.0%) and 10.5% (95% CI, 4.9%–22.6%), respectively, and slightly but not significantly lower for Latin American cases (4.6%; 95% CI, 1.8%–11.6%); see Table S7.

Twenty-five studies with 2324 cases analyzed \( \text{PINK1} \), and the weighted pooled proportion of cases carrying 2 pathogenic \( \text{PINK1} \) mutations was 3.7% (95% CI, 1.3%–10.4%; Fig. 2, Table S3) The majority of mutations (81.8%) were homozygous (95% CI, 56.1%–100.0%; Table S8b). The proportion of familial cases with mutations was 8.4% (95% CI, 2.2%–32.7%), and the risk ratio of familial compared with sporadic cases was 9.3 (95% CI, 1.7–49.4; \( P = .01 \)). The proportion of consanguineous cases with mutations was 31.1% (95% CI, 12.7%–76.2%; Table S5). Compared with outbred cases, this was a highly significant increase, with a risk ratio of 35.3 (95% CI, 9.6–129.0; \( P < 1 \times 10^{-4} \)). Pathogenic \( \text{PINK1} \) mutations were much more common in Asian patients than in white patients: 13.5% (95% CI, 1.9%–94.9%) versus 0.6% (95% CI, 0.2%–1.6%), with a risk ratio of 20.3 (95% CI, 2.1%–197.7) and a \( P \) value of .01 (Table S7). The proportion of Latin American cases with \( \text{PINK1} \) mutations was similar to the proportion of white cases, namely, 0.9% (95% CI, 0.1%–6.0%; Table S7).

Thirteen hundred fifty-one cases in 15 different studies had been screened for \( \text{PARK7} \) (\( \text{DJ1} \)) mutations (Fig. 3, Table S3). \( \text{PARK7} \) mutations appear to be much rarer than \( \text{PARK2} \) or \( \text{PINK1} \) mutations, with an overall mutation frequency of 0.4% (95% CI, 0.2%–1.0%). The proportion of mutation-positive cases appears marginally higher in familial cases, at 0.8% (95% CI, 0.2%–1.3%), compared with 0.4% in sporadic cases (95% CI, 0.1%–1.0%; see Table S6). However, the risk ratio of 2.1 (0.4–11.6) was not significant (\( P = .4 \)). Sample sizes were too small to

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation 1</th>
<th>Mutation 2</th>
<th>Age</th>
<th>AAO</th>
<th>Ethnicity</th>
<th>Sex</th>
<th>Family history</th>
<th>Onset symptom</th>
<th>Lower limb stiffness/rididity</th>
<th>Symmetrical resting tremor</th>
<th>Lower limb dystonia</th>
<th>Lower limb stiffness/rididity</th>
<th>Lower limb tremor and pain</th>
<th>Lower limb stiffness/rididity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK2</td>
<td>42P</td>
<td>Dup. X3</td>
<td>49</td>
<td>37</td>
<td>Welsh</td>
<td>Male</td>
<td>None</td>
<td>Stiffness/rigidity</td>
<td>Lower limb tremor</td>
<td>Symmetrical</td>
<td>Lower limb stiffness/rididity</td>
<td>Lower limb tremor and pain</td>
<td>Lower limb stiffness/rididity</td>
<td></td>
</tr>
<tr>
<td>PARK2</td>
<td>c.154delA frameshift</td>
<td>R275W</td>
<td>58</td>
<td>35</td>
<td>Welsh</td>
<td>Male</td>
<td>None</td>
<td>Stiffness/rigidity</td>
<td>Lower limb tremor</td>
<td>Symmetrical</td>
<td>Lower limb stiffness/rididity</td>
<td>Lower limb tremor and pain</td>
<td>Lower limb stiffness/rididity</td>
<td></td>
</tr>
<tr>
<td>PARK2</td>
<td>Del. X2-3 frameshift</td>
<td>Del. X2</td>
<td>49</td>
<td>8</td>
<td>Welsh</td>
<td>Male</td>
<td>1 Sibling</td>
<td>Symmetrical</td>
<td>Lower limb tremor</td>
<td>Lower limb stiffness/rididity</td>
<td>Lower limb tremor and pain</td>
<td>Lower limb stiffness/rididity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARK2</td>
<td>c.438del4A frameshift</td>
<td>Del. X2</td>
<td>53</td>
<td>20</td>
<td>British</td>
<td>Male</td>
<td>None</td>
<td>Symmetrical</td>
<td>Lower limb tremor</td>
<td>Lower limb stiffness/rididity</td>
<td>Lower limb tremor and pain</td>
<td>Lower limb stiffness/rididity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARK2</td>
<td>Dup X3</td>
<td>Del X2</td>
<td>50</td>
<td>20</td>
<td>British</td>
<td>Female</td>
<td>None</td>
<td>Symmetrical</td>
<td>Lower limb tremor</td>
<td>Lower limb stiffness/rididity</td>
<td>Lower limb tremor and pain</td>
<td>Lower limb stiffness/rididity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PINK1</td>
<td>L347P</td>
<td>Dup X7</td>
<td>58</td>
<td>29</td>
<td>Filipino</td>
<td>Female</td>
<td>None</td>
<td>Symmetrical</td>
<td>Lower limb tremor</td>
<td>Lower limb stiffness/rididity</td>
<td>Lower limb tremor and pain</td>
<td>Lower limb stiffness/rididity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LRRK2</td>
<td>G2019S</td>
<td>Normal</td>
<td>37</td>
<td>26</td>
<td>British</td>
<td>Female</td>
<td>None</td>
<td>Symmetrical</td>
<td>Lower limb tremor</td>
<td>Lower limb stiffness/rididity</td>
<td>Lower limb tremor and pain</td>
<td>Lower limb stiffness/rididity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2. Pathogenic mutations identified with descriptive clinical features

*Parents unaffected. AAO, age at onset. More detailed clinical descriptions can be found in the supplementary material.
compare PARK7 mutation frequencies across different ethnic groups.

Discussion

We present the results of a comprehensive screening study of all 3 EOPD genes and LRRK2 G2019S in a large UK EOPD cohort, together with a systematic review of previous studies. Previously, high mutation frequencies have been reported for PARK2, PINK1, and DJ1 in UK EOPD patients. No cases with pathogenic mutations were identified in our community-based study. Although samples with high ascertainment are desirable for accurate genetic epidemiology, the rarity of EOPD mutations in the Cardiff cohort indicates that local community-based studies may be underpowered. The similar rates in Wales and the United Kingdom indicate that referral bias from specialist centers is not likely to have a significant effect. Our study confirms the previous reports of an increased likelihood of pathogenic mutations in patients with an earlier age of onset, with 30% of patients with age at onset < 30 years having pathogenic mutations in known genes.
Duplication of PARK2 exon 3, deletion of exon 2, and the joint deletion of exons 2 and 3 were first reported in European families in 2000 and are relatively common.\textsuperscript{10,13} Duplication of exon 7 occurs less frequently.\textsuperscript{23,24} Two small deletions, each resulting in a codon frameshift, have also been found in our study and have been reported recurrently in Europe. We identified a single base-pair deletion in exon 2 of PARK2 (c.255delA) leading to a premature stop codon insertion (N52fsX8)\textsuperscript{22,25,26} —once in the heterozygous state and once in a compound heterozygous state in combination with R275W. The second small deletion involves 40 base pairs in exon 3 (c.438-477del40) and is thought to result in aberrant exon splicing.\textsuperscript{27} We also discovered 2 compound heterozygous point mutations in PARK2, the R275W missense mutation, which has been widely reported and is thought to be the most prevalent PARK2 mutation in Europe,\textsuperscript{23,24} and R42P.\textsuperscript{28} The PINK1 point mutation L347P appears to be restricted and common in Filipinos.\textsuperscript{12,29,30} Parkin, PINK1, and DJ-1 proteins have been shown to be involved in mitochondrial function,\textsuperscript{31} and recent data suggest that they may have complementary functions.\textsuperscript{23,32,33} Compound heterozygous mutations across several PARK genes have been described previously\textsuperscript{34–36}; however, in our study no case was found to harbor digenic mutations.

We identified 1 sporadic case with the G2019S mutation in LRRK2. Although this mutation more commonly results in typical late-onset PD, it can also cause PD at a much younger age.\textsuperscript{37} In this cohort of EOPD cases, it was found as frequently as PINK1 mutations, confirming recent findings by Alcalay and colleagues.\textsuperscript{38} Interestingly, this patient presented with typical clinical PD, including nonmotor features, and did not have the early dystonia seen in some carriers of pathogenic mutations in autosomal recessive disease genes.

To put our findings into context, we undertook a systematic review assessing the proportion of PARK2, PINK1, PARK7, LRRK2 mutations in EOPD patients.
and PARK7 mutations were significantly higher in familial patients than in sporadic patients. About 82% of familial EOPD patients did not have mutations in PARK2, PINK1, or PARK7. LRRK2 mutations also appeared to be a relatively rare cause of EOPD. Recently, ATP13A2, PLA2G6, FBXO7, and Spatacsin have been described as additional autosomal

<table>
<thead>
<tr>
<th>Study</th>
<th>Total sample</th>
<th>percentage (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abou–Steiman (2003)</td>
<td>185</td>
<td>0.54 (0.10, 3.00)</td>
</tr>
<tr>
<td>Haguo (2003)</td>
<td>107</td>
<td>0.93 (0.17, 5.10)</td>
</tr>
<tr>
<td>Hedrich (2004)</td>
<td>100</td>
<td>0.00 (0.00, 3.70)</td>
</tr>
<tr>
<td>Djarmati (2004)</td>
<td>75</td>
<td>0.00 (0.00, 4.87)</td>
</tr>
<tr>
<td>Tan (2004)</td>
<td>40</td>
<td>0.00 (0.00, 8.75)</td>
</tr>
<tr>
<td>Lockhart (2004)</td>
<td>41</td>
<td>0.00 (0.00, 8.57)</td>
</tr>
<tr>
<td>Hering (2004)</td>
<td>104</td>
<td>0.96 (0.17, 5.25)</td>
</tr>
<tr>
<td>Lockhart (2004)</td>
<td>49</td>
<td>0.00 (0.00, 7.27)</td>
</tr>
<tr>
<td>Klein (2005)</td>
<td>65</td>
<td>0.00 (0.00, 5.58)</td>
</tr>
<tr>
<td>Guo (2008)</td>
<td>29</td>
<td>3.45 (0.61, 17.18)</td>
</tr>
<tr>
<td>Macedo (2009)</td>
<td>187</td>
<td>0.53 (0.09, 2.97)</td>
</tr>
<tr>
<td>Lee (2009)</td>
<td>66</td>
<td>0.00 (0.00, 5.50)</td>
</tr>
<tr>
<td>Tarantino (2009)</td>
<td>40</td>
<td>2.50 (0.44, 12.88)</td>
</tr>
<tr>
<td>Guo (2010)</td>
<td>127</td>
<td>0.00 (0.00, 2.94)</td>
</tr>
<tr>
<td>Cardiff (2011)</td>
<td>136</td>
<td>0.00 (0.00, 2.75)</td>
</tr>
<tr>
<td>Random Overall</td>
<td></td>
<td>0.40 (0.20, 1.00)</td>
</tr>
</tbody>
</table>

FIG. 3. Forest plot showing percentage of PARK7 mutation-positive cases and 95% confidence intervals for each study included in the systematic review. The right-hand columns show per-study proportions of mutation-positive cases for PARK7 (%) and 95% confidence intervals. The overall proportion, weighted in a random-effects model, is 0.4% (95% CI, 0.2%–1.0%) and is denoted by a gray diamond and dotted line. Gray areas are in proportion to the weighting of each study, and black bars show confidence intervals. The number of cases in each study is shown as well.
recessive EOPD genes; however, the mutations in these genes are likely to be rare and largely restricted to patients with atypical clinical and neuroimaging features. Some of the familial clustering of EOPD may be related to environmental factors, although it is also likely that there are further Mendelian genes that remain to be identified in EOPD.

Acknowledgments: We thank Roger Harbord for his statistical advice on the meta-analysis. We also thank the Queen Square Brain Bank, UCL Institute of Neurology.

References

Park2, Pink1, Park7, Lrrk2 in EOPD

...