Objective: To determine the motor phenotype of LRRK2 G2019S mutation carriers. LRRK2 mutation carriers were previously reported to manifest the tremor dominant motor phenotype, which has been associated with slower motor progression and less cognitive impairment compared with the postural instability and gait difficulty (PIGD) phenotype.

Design: Cross-sectional observational study.

Setting: Thirteen movement disorders centers.

Participants: Nine hundred twenty-five early-onset Parkinson disease cases defined as age at onset younger than 51 years.

Main Outcome Measures: LRRK2 mutation status and Parkinson disease motor phenotype: tremor dominant or PIGD. Demographic information, family history of Parkinson disease, and the Unified Parkinson’s Disease Rating Scale score were collected on all participants. DNA samples were genotyped for LRRK2 mutations (G2019S, I2020T, R1441C, and Y1699C). Logistic regression was used to examine associations of G2019S mutation status with motor phenotype adjusting for disease duration, Ashkenazi Jewish ancestry, levodopa dose, and family history of Parkinson disease.

Results: Thirty-four cases (3.7%) (14 previously reported) were G2019S carriers. No other mutations were found. Carriers were more likely to be Ashkenazi Jewish (55.9% vs 11.9%; P < .001) but did not significantly differ in any other demographic or disease characteristics. Carriers had a lower tremor score (P = .03) and were more likely to have a PIGD phenotype (92.3% vs 58.9%; P = .003). The association of the G2019S mutation with PIGD phenotype remained after controlling for disease duration and Ashkenazi Jewish ancestry (odds ratio, 17.7; P < .001).

Conclusion: Early-onset Parkinson disease G2019S LRRK2 carriers are more likely to manifest the PIGD phenotype, which may have implications for disease course.
tus was associated with a specific motor phenotype (TD vs postural instability and gait difficulty [PIGD]).

METHODS

SUBJECTS

Probands with PD with age at onset (AAO) younger than 51 years (n=925) were recruited from 13 sites in the Consortium on Risk for Early-Onset Parkinson’s Disease (CORE PD) study.14 Institutional review boards at all participating sites approved the protocols and consent procedures. Two hundred forty-five probands were previously recruited in the Genetic Epidemiology of PD study between 1998 and 2003 and have been previously described.3 Additional probands (n=680) were recruited from 2004 until 2008 based on AAO younger than 51 years and a score higher than 23 on the Mini-Mental State Examination (MMSE).15-17 A requirement introduced to ensure that a reliable history could be obtained. Demographic information; results of a UPDRS12 evaluation in the “on” state, completed by a movement disorders specialist; a validated family history interview of first-degree relatives;18 and results of the MMSE were obtained at a single visit. A blood sample for DNA extraction was sent to the National Institute of Neurological Disorders and Stroke Human Genetics Resource Center DNA and Cell Line Repository (http://ccr.coriell.org). All examiners were unaware of the genetic status of the participants. All probands were asked about Jewish ancestry, and the 680 probands recruited in the CORE PD study were asked specifically about AJ descent; however, since 90% of Jewish individuals in the United States are Ashkenazi, we considered all Jewish individuals to be AJ.19 Participants were considered AJ only if all 4 grandparents were AJ.

Probands were classified into motor subtypes based on previously described methods: TD, PIGD, or intermediate.20 Based on the UPDRS, we computed a mean score of 8 tremor items (self-report of tremor, chin tremor, right and left arm tremor, and less likely to have the TD phenotype.

Probands who underwent surgery (pallidotomy, thalamotomy, fetal transplantation, or deep brain stimulation) prior to installment of the probands with disease duration longer than 5 years. In a separate analysis, we included only probands who were not taking levodopa, regardless of disease duration. Given the high proportion of AJ heritage among LRRK2 carriers in previous studies, analyses were repeated separately for all 126 AJ probands. To assess for a potential confounding effect of parkin, we conducted analyses excluding all parkin mutation carriers. In a separate analysis, we excluded probands who underwent surgery (pallidotomy, thalamotomy, fetal transplantation, or deep brain stimulation) prior to the current evaluation.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

Among 925 probands tested, 34 (3.7%) carried a G2019S mutation. Fourteen (41.2%) of these were previously reported.3 One carrier, who was AJ, was a G2019S homozygote. None of the other pathogenic mutations (R1441C, Y1699C, and I2020T) was found. Carriers and noncarriers had similar AAO (range, 13-50 years), disease duration, age at examination, and UPDRS-III and MMSE scores. Carriers were more likely to report AJ ancestry (55.9% vs 11.9%; P<.001), but not more likely to report a first-degree relative with PD than noncarriers. Carriers were more likely to manifest the PIGD phenotype and less likely to have the TD phenotype.

Complete UPDRS scores required to compute PIGD and tremor scores were available on 691 probands, 26 of whom were carriers. Demographic and disease characteristics of carriers and noncarriers with complete UPDRS (n=691) data are presented in Table 2. The remaining probands were missing either the entire UPDRS evaluation (n=35) or items on the UPDRS-II (n=134) or UPDRS-III (n=65). When motor phenotype was computed based only on the UPDRS-III score (n=825, G2019S carriers=29), carrier status was again associated with higher prevalence of PIGD after adjustment for AJ ancestry and disease duration (odds ratio [OR], 16.4; 95% CI, 2.1-127.8; P=.008).

Because of the strong association between PIGD phenotype and G2019S carrier status, we compared demographic and disease characteristics of probands with PIGD and TD (excluding the probands with the intermediate subtype, n=92) (Table 2). Probands with PIGD were older,
had a longer disease duration, higher UPDRS-III scores and daily levodopa doses, and lower MMSE scores than probands with TD. When we compared G2019S carriers with PIGD (n=24) with noncarrier probands with PIGD (n=392), there was no significant difference between groups in demographic and disease severity parameters. We did not compare G2019S carriers with TD or the intermediate subtype with noncarriers because we found only 1 carrier in each of these motor phenotype groups.

In univariate logistic regression models, G2019S was significantly associated only with AJ ancestry and PIGD motor phenotype. In the final multivariate logistic regression model including 691 cases, the association of G2019S carrier status with PIGD motor phenotype remained, after adjustment for AJ ancestry and disease duration (Table 3). Total daily dose of levodopa, AAO, and family history of PD were not associated with G2019S mutation status in either the univariate or multivariate model. After adjustment for disease duration, the association between PIGD and G2019S remained when analyses were performed in 81 AJ individuals and 610 non-AJ individuals separately (AJ: OR, 9.9; 95% CI, 1.8-53.0; P=.008; non-AJ: all G2019S carriers had PIGD; Fisher exact test, P=.004), confirming that the association is not dependent on ethnic background.

Because of the association of PIGD with longer disease duration (Table 2), we examined the relationship of PIGD with disease duration separately in G2019S carriers and noncarriers. For this purpose, we stratified the probands into tertiles of disease duration (<6, 6-13, and >13 years). Among noncarriers, the prevalence of the PIGD phenotype increased with disease duration from 41.3% (107 of 259) to 61.8% (135 of 215) to 78.5% (150 of 191). In contrast, among carriers of the G2019S mutation, all but 2 subjects, both in the lowest tertile, had the PIGD phenotype, so that the prevalence in the 3 duration tertiles was 81.8% (9 of 11), 100% (8 of 8), and 100% (7 of 7). A consequence of this pattern is that the association between PIGD and mutation status was restricted to the shortest disease duration tertile (OR, 15; 95% CI, 2.4-92.9; P=.004).

When only probands with disease duration of 5 years or less were analyzed (n=212, 9 of whom were G2019S carriers), adjusting for AJ ancestry in a logistic regression model, the association was significant (OR, 15.7; 95% CI, 2.1-119.6; P=.008). In a separate analysis, when only probands who were not taking levodopa were assessed (n=188, 6 of whom were G2019S carriers), the association held (Fisher exact test, P=.04). In an analysis excluding all parkin carriers, including 28 homozygotes/compound heterozygotes and 37 heterozygotes, the association between PIGD and G2019S status was unchanged (OR, 17.6; 95% CI, 3.8-82.8; P<.001). There was 1 G2019S carrier who also carried a heterozygous mutation in the parkin gene. The association between carrier status and PIGD held after excluding 150 probands who underwent brain surgery (pallidotomy, thalamotomy, fetal transplantation, or deep brain stimulation) prior to the current evaluation (OR, 5.3; 95% CI, 1.3-18.7; P<.009).

### Table 2. Comparison of Demographic and Clinical Features Between 599 Cases With PIGD and TD With Complete UPDRS Scores

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>TD (n = 183)</th>
<th>P</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G2019S carrier, No. (%)</td>
<td>24 (5.8)</td>
<td>1 (0.5)</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>41.8 (6.5)</td>
<td>42.1 (6.8)</td>
<td>.52</td>
<td></td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>12.3 (8.0)</td>
<td>7.5 (6.0)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>UPDRS-III score</td>
<td>22.1 (13.0)</td>
<td>18.6 (8.9)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Daily levodopa dose, mg</td>
<td>578 (518)</td>
<td>280 (344)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>175 (42.1)</td>
<td>158 (31.7)</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>AJ, No. (%)</td>
<td>46 (11.6)</td>
<td>26 (14.2)</td>
<td>.17</td>
<td></td>
</tr>
<tr>
<td>Family history of PD, No. (%)</td>
<td>67 (16.4)</td>
<td>22 (12.6)</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Report of hallucinations, No. (%)</td>
<td>40 (9.7)</td>
<td>4 (2.2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AAO, age at onset; AJ, Ashkenazi Jewish; MMSE, Mini-Mental State Examination; PD, Parkinson disease; PIGD, postural instability and gait difficulty; TD, tremor dominant; UPDRS, Unified Parkinson’s Disease Rating Scale.

**a**Excluding 92 cases with intermediate phenotype, only 1 of whom was a G2019S carrier.

**b**Score of 2 or higher on the second question (thought disorder question) on the UPDRS-I questionnaire.
Previous reports have suggested that LRRK2 mutations may be associated with tremor in PD. In fact, the protein encoded by LRRK2 was named dardarin, a term derived from dardara, the Basque word for tremor. The largest LRRK2 sample to date found that the core features of carriers included asymmetrical, tremor predominant parkinsonism; however, the UPDRS scores were not available and TD and PIGD scores were not calculated. Herein, when we tested the association on a large EOPD sample evaluated with the UPDRS, the G2019S mutation carriers had lower tremor scores on the UPDRS and were more likely to manifest the PIGD motor phenotype than noncarriers. Because the PIGD phenotype is associated with longer disease duration, we examined whether the greater prevalence of PIGD in carriers in our study was due to longer disease duration. Duration was similar in carriers and noncarriers, allowing us to reject this explanation. LRRK2 G2019S and PIGD phenotype were significantly associated in AJ and non-AJ groups separately, supporting the generalizability of the findings.

To our knowledge, only 1 other study of 187 EOPD cases computed the TD and PIGD motor subtype scores. None of the subjects included in that study carried the G2019S mutation. Fifty percent of the cases had PIGD, similar to the noncarriers in our study. While only EOPD cases were included in this study, limiting generalizability, the effect of age on the presence of PIGD is not as apparent in this sample (mean age, 52.3 years), allowing us to detect a difference among carriers vs noncarriers of G2019S.

Previous studies of late-onset PD that did not define groups by genotype have shown that patients with PD with the PIGD phenotype have a more severe form of PD than those with the TD phenotype, as manifested by a higher proportion of patients with dementia and greater severity as defined by higher UPDRS scores. While most studies of PIGD evaluated PD cases with AAO older than 51 years, 1 study in which 50% (n = 200) of the participants had an AAO younger than 51 years showed a significant association between PIGD phenotype and disease severity (defined by Hoehn and Yahr scale) and poor cognition. In general, the PIGD phenotype has been associated with a faster rate of cognitive decline and is found to be overrepresented in patients with PD with dementia and in patients with dementia with Lewy bodies.

In our study, PIGD was associated with a more severe clinical course than TD, as indicated by a higher UPDRS-III score, higher levodopa dose, and lower MMSE score. However, although G2019S carriers were more likely than noncarriers to have the PIGD motor phenotype, carriers and noncarriers were indistinguishable in terms of each of these measures. Whether the adverse prognosis associated with PIGD applies to G2019S carriers with a PIGD phenotype is unknown.

The major limitation of this study is that it is cross-sectional, and the effect of G2019S on disease progression cannot be assessed directly. While 925 probands were examined, results of the UPDRS-III evaluation were available on 825 subjects, and results of the complete UPDRS evaluation, required for motor phenotyping, were available on 691. Given that our results were similar when applied to the entire data set and to those who had the complete UPDRS evaluation, this is not likely to be a significant confounder.

Another potential limitation of our study is that only 34 G2019S carriers were identified. Therefore, larger samples with broader representation of different ethnic groups would be valuable. The only cognitive assessment obtained, the MMSE, detected cognitive differences between probands with PIGD and TD but may be too insensitive to detect subtle differences between G2019S carriers and noncarriers. Since only G2019S mutation carriers were detected, these results may not be generalized to all LRRK2 mutations. However, G2019S probably accounts for 90% of the known pathogenic mutations.

To further test the association between G2019S carrier status and motor phenotype, a long-term follow-up on a large sample of carriers is required. A longitudinal study including a detailed motor and cognitive examination will confirm the prognosis of mutation carriers.

**Table 3. Logistic Regression Model of the Association Between G2019S Carrier Status and PD Clinical Features in 891 Cases With Complete UPDRS Data**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Unadjusted OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>1.0 (0.95-1.03)</td>
<td>.70</td>
<td>1.09 (1.01-1.17)</td>
<td>.02</td>
</tr>
<tr>
<td>AJ ancestry</td>
<td>9.4 (4.6-19.0)</td>
<td>&lt;.001</td>
<td>19.6 (7.9-49.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PIGD phenotype</td>
<td>8.4 (2.0-35.7)</td>
<td>.01</td>
<td>17.7 (3.8-83.1)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: AJ, Ashkenazi Jewish; CI, confidence interval; OR, odds ratio; PD, Parkinson disease; PIGD, postural instability and gait difficulty; UPDRS, Unified Parkinson’s Disease Rating Scale.

a Analyses were performed with and without 1 G2019S homozygote proband. There were no significant differences.

b Age at onset, total daily levodopa dose, family history, and age at examination were excluded from the final model because of lack of significance. The final model included disease duration, AJ ancestry, and PIGD phenotype.

**Author Affiliations:** Departments of Neurology (Drs Alcalay, Tang, Rosado, Louis, Waters, Fahn, Frucht, Ford, and Marder and Ms Mejia-Santana) and Pathology and Cell Biology (Dr Clark), Taub Institute for Research on Alzheimer’s Disease and the Aging Brain (Drs Tang, Verbitsky, Louis, Caccappolo, Clark, and Marder, Mr Kiselev, and Ms Ross), Gertrude H. Sergievsky Center (Drs Louis, Cote, Ottman, and Marder), College of Physi-
cians and Surgeons, Center for Human Genetics (Dr Clark), and Department of Epidemiology, Mailman School of Public Health (Drs Louis and Ottman), Columbia University, Department of Psychiatry, Columbia University Medical Center (Dr Marder), The Alan and Barbara Mirken Department of Neurology, Beth Israel Medical Center (Dr Bressman), and New York State Psychiatric Institute, Data Coordinating Center (Dr Andrews), New York, and Department of Neurology, Albert Einstein College of Medicine, Bronx (Dr Bressman); Department of Neurology/Movement Disorder Section (Dr Comella), Rush University, and Department of Neurology, Northwestern University. Feinberg School of Medicine (Drs Rezak and Novak), Chicago, and Department of Neurology, NorthShore University HealthSystem, Evanston (Drs Rezak and Novak), Illinois; Parkinson’s Disease and Movement Disorders Center, Pennsylvania Hospital (Dr Colcher), and Department of Neurology, University of Pennsylvania Health System (Dr Siderowf), Philadelphia; The Institute for Neurodegenerative Disorders, New Haven, Connecticut (Dr Jennings); Struthers Parkinson’s Center, Park Nicotol Clinic, Golden Valley, Minnesota (Dr Nance); Dr John T. Macdonald Foundation, Department of Human Genetics, Miami Institute for Human Genomics, Miller School of Medicine, University of Miami, Miami, Florida (Dr Scott); Parkinson’s Institute, Sunnyvale, California (Dr Tanner); Marshfield Clinic, Department of Neurology, Marshfield (Dr Mickel), and Medical College of Wisconsin, Milwaukee (Dr Hiner); Parkinson’s Disease and Movement Disorders Center of NeuroHealth, Warwick (Dr Friedman), and Department of Clinical Neurosciences, The Warren Alpert School of Medicine of Brown University, Providence (Dr Friedman), Rhode Island; Department of Neurology, College of Medicine, University of Tennessee Health Science Center, Memphis (Dr Pfeiffer); Morris K. Udall Parkinson’s Disease Research Center of Excellence and Department of Neurology/Movement Disorder Section (Dr Comella), Rush University, and Department of Neurology, NorthShore University HealthSystem, Evanston (Dr Comella), and Department of Neurology, NorthShore University HealthSystem, Evanston (Dr Comella).

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Correspondence: Karen S. Marder, MD, MPH, Department of Neurology, Columbia University, 622 W 168th St, 19th Floor, New York, NY 10032 (ksm1@columbia.edu).

Author Contributions: Dr Marder had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Alcalay, Mejia-Santana, Nance, Tanner, Caccappolo, Ottman, and Marder. Acquisition of data: Rosado, Verbitsky, Kisselev, Ross, Comella, Colcher, Jennings, Nance, Bressman, Scott, Tanner, Mickel, Andrews, Waters, Fahn, Cote, Frucht, Ford, Novak, Friedman, Pfeiffer, Marsh, Hiner, Siderowf, Caccappolo, Ottman, Clark, and Marder. Analysis and interpretation of data: Tang, Louis, Nance, Tanner, Novak, Clark, and Marder. Drafting of the manuscript: Alcalay, Ross, Rezak, Clark, and Marder. Critical revision of the manuscript for important intellectual content: Mejia-Santana, Tang, Rosado, Verbitsky, Kisselev, Louis, Comella, Colcher, Jennings, Nance, Bressman, Scott, Tanner, Mickel, Andrews, Waters, Fahn, Cote, Frucht, Ford, Novak, Friedman, Pfeiffer, Marsh, Hiner, Siderowf, Caccappolo, Ottman, Clark, and Marder. Statistical analysis: Alcalay, Tang, Louis, Scott, and Marder. Obtained funding: Fahn, Clark, and Marder. Administrative, technical, and material support: Mejia-Santana, Rosado, Verbitsky, Kisselev, Ross, Colcher, Bressman, Mickel, Andrews, Cote, Ford, Rezak, Friedman, Siderowf, and Caccappolo. Study supervision: Ottman and Marder.

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