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%; \( P \leq 0.001 \)) 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 \( (\text{odds ratio}, 17.7; P < .001) \).

Conclusion: Early-onset Parkinson disease G2019S LRRK2 carriers are more likely to manifest the PIGD phenotype, which may have implications for disease course.

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of the required items were not classified as having TD or PIGD.

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.1-4 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).15-16 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;16 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.16 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 right and left leg tremor and right and left arm action tremor on examination) as well as a mean score of 5 PIGD items (self-report of falling, freezing, and walking difficulty, gait and postural instability on examination). A ratio of tremor score divided by PIGD score was then computed. Tremor dominant was defined as a ratio more than 1.5 and PIGD, less than 1. Proband type was computed based only on the UPDRS-III score.15-16

Molecular Genetic Analysis

Genotyping of LRRK2 mutations of 245 probands in the Genetic Epidemiology of PD study has been described previously, using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (Sequenom, San Diego, California). An additional 193 DNA samples from individuals recruited in the CORE PD study were genotyped using the same assay. We analyzed all samples for mutations G2019S, I2020T, Y1699C, and I1122V and L1114L.21 DNA samples from the remainder of the probands recruited in the CORE PD study (n=487) were analyzed using a previously described genotyping chip21 (Asper Biotech, Tartu, Estonia). Thirty individuals who carried G2019S detected by MALDI-TOF were also examined using the genotyping chip without knowledge of the MALDI-TOF results and were confirmed. In addition to G2019S, all samples analyzed by the genotyping chip were also examined for the mutations R1441C, I1122V, and L1114L.

RESULTS

Statistical Analyses

The t test, χ² test, and Fisher exact test were used as appropriate to compare continuous and categorical variables between G2019S carriers and noncarriers. Univariate logistic regression models were constructed to examine the association between LRRK2 G2019S mutation status (dependent variable) and Jewish ancestry, total daily dose of levodopa, family history of PD in a first-degree relative, AAO, disease duration, age at examination, and PIGD or TD subtypes. A multivariate logistic regression model was then constructed including all significant associations. Disease duration was added to the model because of the expected association between disease duration and disease severity.

Since disease duration is highly associated with severity of motor and cognitive symptoms in PD,20 we performed additional analyses comparing probands with longer vs shorter disease duration (tertiles) to determine the effect of disease duration on the association of G2019S and motor subtype. We repeated the analysis on all probands with disease duration less 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,3 analyses were repeated separately for all 126 AJ probands.

Demographic Characteristics

Among 925 probands tested, 34 (3.7%) carried a G2019S mutation. Fourteen (41.2%) of these were previously reported.1 One carrier, who was AJ, was a G2019S homoyzgote. 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 1.

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 between PIGD and mutation status was restricted to the shortest disease duration tertile (OR, 15; 95% CI, 2.1-119.6; \(P = .008\)). In a separate analysis, when only probands who were not taking levodopa were assessed (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, 3.8-82.8; \(P = .004\)). 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, 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, 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, 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, \(P = .04\)). 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Previous studies 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.

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