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Motor phenotype of *LRRK2* G2019S carriers in Early Onset Parkinson Disease

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Abstract

Objective—To determine the motor phenotype of *LRRK2* G2019S mutation carriers

Background—*LRRK2* mutation carriers were previously reported to manifest the tremor-dominant (TD) motor phenotype, which has been associated with slower motor progression and less cognitive impairment compared to the postural instability gait difficulty (PIGD) phenotype.

Design—Cross sectional observational study

Setting—13 movement disorders centers

Participants—925 Early Onset Parkinson Disease (EOPD) cases defined as age at onset (AAO) ≤ 50 .

Main Outcome Measures—*LRRK2* mutation status and PD motor phenotype: TD or PIGD

Methods—Demographic information, family history of PD (FHPD), and the Unified Parkinson Disease Rating Scale (UPDRS) 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 (AJ) ancestry, levodopa dose, and FHPD.

Results—34 cases (3.7%) (14 previously reported) were G2019S carriers. No other mutations were found. Carriers were more likely to be AJ (55.9% vs. 11.9% $p < 0.001$), but did not significantly differ in any other demographic or disease characteristics. Carriers had a lower tremor score ($p = 0.026$) and were more likely to have a PIGD phenotype (92.3% vs. 58.9% $p = 0.003$). The association of the G2019S mutation with PIGD phenotype remained after controlling for disease duration and AJ (OR = 17.7, $p < 0.001$).

Conclusion—EOPD G2019S *LRRK2* carriers are more likely to manifest the PIGD phenotype, which may have implications for disease course.

Introduction

Mutations in *LRRK2* (Leucine-Rich Repeat Kinase-2) (PARK8) are associated with both sporadic and familial Parkinson's disease (PD). The most frequently reported *LRRK2* mutation, G2019S (nt. 2877510G→A) is found in up to 1% of sporadic and 4% of familial PD cases worldwide.¹ Furthermore, up to 39% of Northern African Arab² and 18.3% of Ashkenazi Jewish (AJ)^{3, 4} PD cases carry the mutation. We and others have shown that the frequency of *LRRK2* mutations is similar in early onset PD (EOPD) and late-onset PD;^{1, 5} however, only small series of *LRRK2* mutation carriers with EOPD have been described.^{3, 6–8}

LRRK2 related parkinsonism is associated with good response to treatment with levodopa and dopamine agonists, but may be complicated by dyskinesia.¹ While the presentation of *LRRK2* related PD is heterogeneous,^{9–11} the largest study to date of *LRRK2* carriers suggested an association between *LRRK2* mutations and the tremor dominant (TD) motor phenotype.¹ However, in that study, the participants' Unified Parkinson's Disease Rating Scale (UPDRS)¹² was not available. Given the potentially favorable prognosis that is associated with TD PD,¹³ we tested this hypothesis on a large sample of EOPD cases with available UPDRS performed by movement disorders specialists.

We determined whether mutation status is associated with a specific motor phenotype (TD versus postural instability and gait difficulty (PIGD)).

Methods

Subjects

PD probands with AAO ≤ 50 (n = 925) were recruited from 13 sites in the 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 (GEPD) study between 1998 and 2003 and have been previously described.³ Additional probands (n=680) were recruited from 2004 until 2008 based on AAO ≤ 50 years and a score ≥ 24 on the Mini-mental State Exam (MMSE^{15, 16, 17}), a requirement introduced to ensure that a reliable history could be obtained. Demographic information, a UPDRS¹² in the “on” state, completed by a movement disorders specialist, a validated family history interview of first-degree relatives¹⁸ and the MMSE were obtained at a single visit. A blood sample for DNA extraction was sent to the NINDS 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 Ashkenazi Jewish descent, however since 90% of Jews in the United States are Ashkenazi, we considered all Jews AJ.¹⁹ Participants were considered AJ only if all four grandparents were AJ.

Probands were classified into motor subtypes based on previously described methodology: tremor dominant (TD), postural instability and gait difficulty (PIGD) or intermediate.²⁰ Based on the UPDRS, we computed a mean score of eight tremor items (self report of tremor, chin tremor, right and left arm tremor, right and left leg tremor and right and left arm action tremor on examination), as well as a mean score of five 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. TD was defined as ratio ≥ 1.5 and PIGD as ≤ 1 . Probands with a ratio between 1–1.5 were classified as intermediate. Individuals with missing data on any of the required items were not classified as TD or PIGD.

Molecular Genetic Analysis

Genotyping of *LRRK2* mutations of 245 probands in the GEPD study has been described previously,³ using Matrix-Assisted Laser Desorption/Ionization Time of Flight (MALDI-TOF) mass spectrometry (Sequenom). An additional 193 DNA samples from individuals recruited in CORE PD were genotyped using the same assay. We analyzed all samples for mutations G2019S, I2020T, R1441C and Y1699C and also assessed the frequency of 2 rare *LRRK2* variants (I1122V, L1114L).

DNA samples from the remainder of the probands recruited in CORE PD (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, I2020T and Y1699C.

Statistical analyses

Student t-test, chi-square, and Fisher exact tests were used as appropriate to compare continuous and categorical variables between G2019S carriers and non-carriers. 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 exam 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,²² 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. 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 (DBS)) 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 non-carriers had similar AAO (range: 13–50 years), disease duration, age at examination, UPDRS-III and MMSE scores. Carriers were more likely to report AJ ancestry (55.9% vs. 11.9%, $p < 0.001$), but not more likely to report a first-degree relative with PD than non-carriers. Carriers were more likely to manifest the PIGD phenotype and less likely to be of 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 non-carriers with complete UPDRS ($n=691$) are presented in Table 1.

The remaining probands were missing either the entire UPDRS ($n=35$), or items on the UPDRS-II ($n=134$) or UPDRS-III ($n=65$). When motor phenotype was computed based only on the UPDRS-III ($n=825$, G2019S carriers = 29) carrier status was again associated with higher prevalence of PIGD after adjustment for AJ ancestry and disease duration (OR 16.4; 95% confidence interval 2.1–127.8, $p=0.008$).

Because of the strong association between PIGD phenotype and G2019S carrier status we compared demographic and disease characteristics of PIGD and TD probands (excluding the intermediate probands, $n=92$) (Table 2). PIGD probands were older, had a longer disease duration, higher UPDRS-III scores and daily levodopa doses, and lower MMSE scores than TD cases. When we compared PIGD G2019S carriers ($n=24$) with non-carrier PIGD probands ($n=392$) there was no significant difference between groups in demographic and disease severity parameters. We did not compare TD or intermediate G2019S carriers to non-carriers because we found only one 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 and 610 non-AJ separately (AJ: OR= 9.9; 95% CI: 1.8–53.0, $p=0.008$. Non AJ: all G2019S carriers were PIGD. Fisher exact p -value=0.004), 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 non-carriers. For this purpose we stratified the probands into tertiles of disease duration (≤ 6 , 6–13, ≥ 13 years). Among non-carriers, the prevalence of the PIGD phenotype increased with disease duration from 41.3% (107/259), to 61.8% (135/215), to 78.5% (150/191). In contrast, among carriers of the G2019S mutation, all but two subjects, both in the lowest tertile, had the PIGD phenotype, so that the prevalence in the three duration tertiles was 81.8% (9/11), 100% (8/8), 100% (7/7). 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, $p=0.004$).

When only probands with disease duration of five 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, $p=0.008$). In a separate analysis, when only probands who were not taking levodopa were assessed ($n=188$, 6 of whom G2019S carriers) the association held, (Fisher exact $p=0.043$). 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, $p<0.001$). Of note, there was one 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 DBS) prior to the current evaluation (OR: 5.3, 95%CI 1.5–18.7, $p<0.009$).

Comment

Previous reports have suggested that *LRRK2* mutations may be associated with tremor in PD.^{1, 23, 24} In fact, the protein encoded by *LRRK2* was named dardarin – a term derived from dardara, the Basque word for tremor.²⁵ The largest *LRRK2* sample to date found that the core features of carriers included asymmetrical, tremor predominant parkinsonism,¹ however the UPDRS scores were not available and TD and PIGD scores were not calculated. Here, when we tested the association on a large EOPD sample evaluated with the UPDRS, the G2019S mutation carriers have lower tremor scores on the UPDRS, and are more likely to manifest the PIGD motor phenotype than non carriers. 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 longer disease duration. Duration was similar in carriers and non-carriers, 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 one other study of 187 EOPD cases computed the TD and PIGD motor subtype scores.²⁶ None of the subjects included in that study carried the G2019S mutation. Fifty percent of the cases were PIGD, similar to the non-carriers in our study. While only EOPD cases were included in this study, limiting generalizability, the effect of age on the presence of PIGD are not as apparent in this sample (mean age 52.3) allowing us to detect a difference among carriers versus non-carriers of G2019S.

Previous studies of late onset PD that did not define groups by genotype have shown that PD patients 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.²² While most studies of PIGD evaluated PD cases with

AAO ≥ 50 , one study in which 50% (n=200) of the participants had an AAO ≤ 50 showed a significant association between PIGD phenotype and disease severity (defined by Hoehn and Yahr scale) and poor cognition.²⁷ In general, the PIGD phenotype has been associated with a faster rate of cognitive decline,²⁸ and is found to be over represented in demented PD patients and in patients with dementia with Lewy bodies.²⁹

In our study, PIGD was associated with 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 non-carriers to have the PIGD motor phenotype, carriers and non-carriers were indistinguishable in terms each of these measures of clinical course. 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, the UPDRS-III was available on 825 subjects, and complete UPDRS, required for motor phenotyping²⁰, was available on 691. Given that our results were similar when applied to the entire dataset 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 PIGD and TD probands, but may be too insensitive to detect subtle differences between G2019S carriers and non-carriers. Since only G2019S mutation carriers were detected, these results may not be generalized to all *LRRK2* mutations. However, the G2019S probably accounts for 90% of the known pathogenic mutations.¹

In order 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 follow up including a detailed motor and cognitive exam will confirm the prognosis of mutation carriers.

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Table 1

Comparison of demographic and clinical features between 691 G2019S carriers and non-carriers on whom complete UPDRS was available

	LRRK2 G2019S carriers (n=26)	LRRK2 non-carriers (n=665)	Significance
Age at onset (years)	42.9 (5.0)	41.7 (6.7)	NS
Age at examination (years)	52.7 (8.4)	52.1 (8.7)	NS
Disease duration (years)	9.8 (7.8)	10.4 (7.6)	NS
Education (years)	15.6 (3.3)	15.6 (2.8)	NS
UPDRS-III	19.7 (13.7)	20.5 (11.7)	NS
Levodopa daily dose (mg)	556 (624)	471 (492)	NS
MMSE score	29.1 (1.6)	29.1(1.6)	NS
Gender (% females)	46.2% (12)	38.2% (254)	NS
Ashkenazi Jewish Ancestry (%)	57.7% (15)	10.1% (67)	p<0.001
First degree family history of PD (% positive)	20.8% (5)	15.3% (99)	NS
First degree family history of PD in AJ (% positive)	21.4% (n=3)	15.2 (n=10)	NS
First degree family history of AD (% positive)	0%	4.9%	NS
Report of hallucinations ¹	3.8% (1)	7.0% (46)	NS
Asymmetric onset (%) ²	88.5% (23)	94.0% (614)	NS
Rest tremor as presenting symptom (%) ²	44.0%(11)	41.5(271)	NS
Mean tremor score ³	2 (2.1)	3.4(3.8)	p=0.026 ⁴
Mean PIGD score ³	4.4 (3.2)	3.4(3.3)	NS
PIGD phenotype	92.3% (24)	58.9% (392)	P=0.003
TD phenotype	3.8% (1)	27.4% (182)	p=0.003

Values are mean (standard deviation) or percent (number)

¹ score of 2 or above on the 2nd question (thought disorder question) on the UPDRS-I questionnaire

² Presenting symptoms as reported by the participants

³ The sum of points received for tremor or PIGD items on the UPDRS respectively

⁴ The 0.8 point difference corresponds to 30% difference

Table 2

Comparison of demographic and clinical features between 599 PIGD and TD cases with complete UPDRS scores¹

	PIGD (n=416)	TD (n=183)	Significance
G2019S carriers	5.8% (24)	0.5% (1)	p=0.002
AAO (years)	41.8 (6.5)	42.1 (6.8)	NS
Age (years)	54.1 (8.9)	49.7 (7.4)	p<0.001
Disease duration (years)	12.3 (8.0)	7.5 (6.0)	p<0.001
Education (years)	15.5 (2.9)	15.7 (2.8)	NS
MMSE	28.9 (1.9)	29.4 (1.1)	p= 0.002
UPDRS-III	22.1 (13.0)	18.6 (8.9)	p<0.001
Daily levodopa dose (mg)	578 (518)	280 (344)	p<0.001
Gender (% female)	42.1% (175)	31.7% (158)	p<0.001
Ashkenazi Jewish	11.1% (46)	14.2% (26)	NS
Family history of PD	16.4% (67)	12.6% (22)	NS
Report of hallucinations ²	9.7% (40)	2.2% (4)	p<0.001

¹ excluding 92 intermediate cases, only one of which is a G2019S carrier

² score of 2 or above on the 2nd question (thought disorder question) on the UPDRS-I questionnaire

Table 3

Logistic regression model of the association between G2019S carrier status¹ and PD clinical features in 691 cases with complete UPDRS data²

	Unadjusted odds ratio	95% Confidence interval	Significance	Adjusted odds ratio	95% Confidence interval	Significance
Disease duration(yr)	1.0	0.95–1.03	p=0.7	1.09	1.01–1.17	p=0.019
Ashkenazi Jewish Ancestry	9.4	4.6–19.0	p<0.001	19.8	7.9–49.6	p<0.001
PIGD phenotype	8.4	2.0–35.7	p=0.013	17.7	3.8–83.1	p<0.001

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

² 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.