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Parkinson Disease Phenotype in Ashkenazi Jews with and without *LRRK2* G2019S mutations

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Abstract

Background—The phenotype of Parkinson disease (PD) patients with and without *LRRK2* G2019S mutations is reported to be similar; however large uniformly evaluated series are lacking.

Objective—To characterize the clinical phenotype of Ashkenazi Jewish (AJ) PD carriers of the *LRRK2* G2019S mutation.

Methods—We studied 553 AJ PD patients, including 65 patients who were previously reported, from three sites (two in New York and one in Tel-Aviv). *GBA* mutation carriers were excluded. Evaluations included the Montreal Cognitive Assessment (MoCA), the Unified Parkinson's Disease Rating Scale (UPDRS), the geriatric depression scale (GDS) and the non-motor symptoms (NMS) questionnaire. Regression models were constructed to test the association between clinical and demographic features and *LRRK2* status (outcome) in 488 newly recruited participants.

Results—*LRRK2* G2019S carriers (n=97) and non-carriers (n=391) were similar in age and age-at-onset of PD. Carriers had longer disease duration (8.6years versus 6.1years, $p<0.001$), were more likely to be women (51.5% versus 37.9%, $p=0.015$) and more often reported first symptoms in lower extremities (40.0% versus 19.2%, $p<0.001$). In logistic models adjusted for age, disease duration, gender, education, and site, carriers were more likely to have lower extremity onset ($p<0.001$), postural instability gait difficulty (PIGD, $p=0.043$) and persistent levodopa response for >5 years ($p=0.042$). Performance on UPDRS, MoCA, GDS and NMS did not differ by mutation status.

Conclusion—PD in AJ-*LRRK2* G2019S mutation carriers is similar to idiopathic PD, but characterized by more frequent lower extremity involvement at onset and PIGD without the associated cognitive impairment.

Keywords

Parkinson; Genetics; *LRRK2*; PIGD

Introduction

Mutations in Leucine-Rich Repeat Kinase 2 (*LRRK2*) were first identified in 2004 as a cause for parkinsonism in families with autosomal dominant transmission.^{1,2} Since then, *LRRK2* mutations and risk variants have been identified in PD patients worldwide.^{3,4} Among PD patients of Ashkenazi Jewish (AJ) descent, 14.8-18.3% carry the G2019S mutation.^{5,6} Age-at-onset (AAO) in mutation carriers varies widely, and is often lower than in non-carriers.^{3,5,7,8} The largest report to date comparing PD phenotype between *LRRK2* carriers and non-carriers was based on 19,376 PD patients of multi-ethnic background, but individual Unified Parkinson's Disease Rating Scale scores were not used in the analysis.³ Additional cohorts have demonstrated that tremor is often a presenting symptom,^{4,9} but other studies have demonstrated that carriers were more likely to have postural instability and gait difficulty (PIGD) and less rest tremor.¹⁰

The *LRRK2* Ashkenazi Jewish consortium was established in 2009 and includes centers in Israel (Tel Aviv Medical Center) and New York (Beth Israel Medical Center and Columbia University Medical Center). The aim of the consortium is to examine the clinical characteristics and genetic modifiers of disease onset in families of PD probands with and without *LRRK2* G2019S mutations. Participants include both previously identified *LRRK2* G2019S carriers and non-carriers and newly screened participants (majority), all of whom underwent an identical screening assessment. Carriers, a subset of non-carriers, and their first-degree relatives underwent an in-depth evaluation. Here, we present the results of the comparison of PD probands with and without G2019S mutations who completed the screening protocol.

Methods

Participants

Five-hundred and fifty-three participants were recruited from three sites. Participants included 488 newly genotyped and 65 previously genotyped participants. We included only the newly recruited participants in the primary analyses because previously genotyped participants were enriched for G2019S mutation carriers (Table 1), had longer disease duration, and were recruited through studies which were enriched for either early-onset PD (Columbia University) or family history of PD (Beth Israel).⁵⁻⁷ Institutional review boards at all participating sites approved the protocols and all participants signed consent prior to any research procedure. Participants were recruited if they reported at least two AJ grandparents and were diagnosed with PD by a movement disorder specialist, based on the UK PD brain bank criteria (except that we did not exclude cases with extensive family history of PD).¹¹ Thirteen (2.7%) participants were aware of their *LRRK2* genetic status from clinical testing or direct-to-consumer testing. All participants were screened for *LRRK2* G2019S mutations.^{5,6} Given the high frequency of *GBA* mutations among AJ, we screened for the common mutations in this population: N370S, L444P, 84GG, IVS2+1, D409G, V394L and R496H.^{12,13} These mutations account for over 95% of *GBA* mutations in AJ.¹⁴ *GBA* mutation carriers, including those who carried both *LRRK2* G2019S and a *GBA* mutation, were excluded from the analyses.

Clinical evaluation

All participants were evaluated using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III),¹⁵ the Montreal Cognitive Assessment (MoCA),¹⁶ performed in either Hebrew¹⁷ or English based on participants' native language), the abbreviated geriatric depression scale (GDS-15¹⁸, higher scores suggest increased likelihood of depression, score >5 indicates clinically important depressive symptoms¹⁹) and the Non-Motor Symptoms (NMS) questionnaire (higher scores indicate more NMS).²⁰ Postural Instability Gait Difficulty (PIGD) phenotype was computed as previously reported^{10,21} for 371 participants with available UPDRS-II and UPDRS-III data. Family history was obtained using a structured family history interview in New York,²² and by report of the proband or an informant in Tel-Aviv. Levodopa equivalent daily doses were calculated using a previously published algorithm combining dopamine agonist daily dose with levodopa daily dose.²³ Participants' phenotype was further characterized with questionnaires completed at the time of examination or chart review by either the treating physicians, or a senior member of the research team. These included questions on the presence of dyskinesia and on sustained response to levodopa for more than five years. In addition, past medical history and symptoms at disease onset were collected by participant self-report.

Statistical Analysis

Demographics and disease characteristics were compared among the three recruitment sites. Demographics, disease characteristics, UPDRS, MoCA, GDS and NMS performance of *LRRK2* carriers and non-carriers were compared using chi-square tests, Fisher's exact and Student's t-tests. Analyses were performed on all participants, and stratified by site (to assess for potential confounders). Regression models were constructed to test the association between clinical and demographic features (predictors) and *LRRK2* status (outcome), adjusted for age, disease duration, gender, education (categorized as with or without post-high-school education) and recruitment site. Finally, analyses were repeated including participants who were previously genotyped (n=553).

Results

Ninety-seven of 488 newly recruited participants (19.9%) carried the G2019S mutation, and this proportion was similar among sites (18.6%-20.5%, $p=0.91$). Three were homozygote G2019S carriers. The phenotype of the homozygote carriers was similar to heterozygote carriers, including their AAO (mean=56.7) and their performance on the UPDRS, MoCA, GDS and NMS". The demographic and disease characteristics of participants from the three sites are presented in Supplementary Table 1. Columbia participants were older than participants at the other two sites ($p<0.001$). Beth Israel participants had lower UPDRS-III scores than participants at the other sites ($p<0.001$). Compared to the NY sites, fewer participants in Tel-Aviv had post-secondary education. They scored lower on the MoCA and were treated with lower daily equivalent dose of levodopa.

Carriers and non-carriers of *LRRK2* G2019S were similar in age, AAO (defined as onset of motor symptoms), UPDRS-III, MoCA, GDS and NMS scores (Table 2). However, carriers were more likely to be women ($p=0.015$), to have a longer disease duration (8.6 years versus 6.0 years, $p<0.001$), and report family history of PD in first-degree relatives. There was no difference between carriers and non-carriers in total NMS score (Table 2) although when individual questions were analyzed, carriers were less likely to report "talking or moving about in sleep as if acting out a dream" (22.8% versus 35.1%, $p=0.026$ Fisher Exact). Carriers were more likely to report lower extremity involvement at onset, and less likely to report any tremor at onset. Of the 38 (40.0%) carriers who reported lower extremity involvement at onset, 14 (14/38, 36.8%) reported leg tremor, 14 (36.8%) reported slow or shuffling gait and the remaining reported stiffness or sustained muscle contraction as their presenting symptom. Carriers were more likely to be classified as PIGD based on their UPDRS, use higher levodopa equivalent daily dose, and more likely to ever experience dyskinesia. Among participants with disease duration longer than five years, carriers were more likely to have sustained good response to levodopa for >5 years.

When analyses were repeated stratified by site, there were no significant changes in the results, with the exception of GDS scores at Beth Israel (carriers were more likely to score higher on the GDS scale, 5.8 versus 3.2, $p=0.003$) and MoCA scores in Tel Aviv (carriers were more likely to score higher on the MoCA, 25.1 versus 23.7, $p=0.028$).

In logistic models adjusted for age, duration of motor symptoms, gender, education and recruitment site, carriers were more likely to have lower extremity onset ($p<0.001$), PIGD phenotype ($p=0.043$) and persistent levodopa response for >5 years ($p=0.042$) as assessed by their treating clinicians. Levodopa equivalent daily dose, performance on UPDRS-III, MoCA, GDS, NMS and presence of dyskinesia did not differ by mutation status in the adjusted model. When regression analyses included all 553 participants (including those previously genotyped), results were similar.

Because of the association between *LRRK2* G2109S mutations and PIGD phenotype and the lack of association between MoCA and UPDRS performance with *LRRK2* mutation status, we tested the association between PIGD phenotype and MoCA and UPDRS performance and levodopa equivalent daily dose separately in carriers and non-carriers. Non-carriers who manifested the PIGD phenotype scored lower on the MoCA (24.4 versus 25.7, $p=0.003$), had higher UPDRS-III scores (22.2 versus 16.5, $p<0.001$) and were treated with higher levodopa equivalent daily dose (433mg versus 237mg, $p<0.001$) than those without PIGD phenotype. Similar associations, however, were not observed among *LRRK2* carriers (MoCA: 25.2 versus 25.1, $p=0.879$; UPDRS-III: 19.6 versus 17.9, $p=0.576$; levodopa equivalent daily dose: 465mg versus 261mg, $p=0.171$).

Discussion

In this systematically assessed cohort that included only Ashkenazi Jews, we found that carriers and non-carriers had many similarities to idiopathic PD.^{3,9} However, some differences in the demographics and disease characteristics exist and may suggest a different pathophysiology in mutation carriers. Carriers were more likely to be women, while idiopathic PD is more prevalent in men. This gender effect was observed in some,^{5,24,25} but not all previous reports.⁹ This suggests that penetrance modifiers in this group may be different from penetrance modifiers in idiopathic PD.²⁵ Like Healy et al,³ we have found that carriers' severity of extrapyramidal signs (Hoehn and Yahr in Healy et al, UPDRS-III scores in this study) was similar to non-carriers,^{3,9,10} and dyskinesias were similarly present in both groups after adjusting for disease duration and levodopa equivalent daily dose.²⁶ Similarly, cognitive screens (Mini Mental State Exam in Healy et al, MoCA in this study) did not differ between carriers and non-carriers. Both studies report frequent early lower extremity involvement. Healy and colleagues reported longer latency between disease onset and first fall among carriers compared to non-carriers. Latency between disease onset and first fall was not assessed in this study. Here, carriers were more likely to maintain a sustained response to levodopa than non-carriers for over five years. Longitudinal follow up is required to clarify whether the sustained response to levodopa for >5 years is a result of earlier levodopa treatment in carriers, or a marker of a motor phenotype, which includes a long standing sustained response to levodopa.

As we have reported in another cohort,¹⁰ carriers were more likely to manifest the PIGD motor phenotype. Unlike non-carriers, we did not find increased cognitive impairment in our *LRRK2*-PD patients classified as PIGD. This suggests that PIGD in *LRRK2* does not conform to prior characterization of this PD subtype, which is reportedly associated with greater cognitive impairment, poorer response to levodopa, and more rapid progression.^{21,27,28} A possible explanation may involve compensatory mechanisms and enhanced functional connectivity present in this genetic form of PD.²⁹

In addition, *LRRK2*-PD carriers were more likely to present with lower extremity involvement, and these findings reaffirm previously reported associations.³ In fact, gait alteration has been reported in *LRRK2* carriers prior to PD diagnosis.³⁰ The anatomical correlates of these clinical observations are unknown. While there is no evidence for somatotopy (legs versus arms versus face innervation) in the substantia nigra pars compacta, there is evidence for somatotopy in the globus pallidus, putamen and the subthalamus.³¹ To our knowledge, all reported G2109S PD autopsies came from patients with advanced PD, and therefore, clinical-anatomical correlation cannot be obtained.³²

When data from all three recruitment sites were compared, we found a similar frequency of mutation carriers and reported family history of PD in first-degree relatives among sites. This reflects the homogeneity of our PD sample, which includes only AJ-PD participants

without other known genetic risk factors, such as *GBA* mutations, despite geographic differences between Israel and the United States. Differences between sites including age at recruitment, UPDRS, MoCA, education and levodopa dose on other hand may reflect diverse referral, cultural and practice effects and highlight the need for large studies that mitigate these local effects even in the setting of a uniform protocol.

The major strengths of our study are the homogenous ethnic group, and the large sample size with uniform clinical evaluation methods employed. The cross-sectional design, rather than a prospective longitudinal design, does not allow comparison of disease progression.

Future studies that include more detailed clinical exams, including gait and non-motor assessments will help determine whether there are specific features of gait and cognition that differ between groups. Longitudinal follow up is required to compare disease course between carriers and non-carriers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Authors' role:

Roy N. Alcalay study concept and design, acquisition of data, analysis and interpretation, drafting manuscript; Anat Mirelman study concept and design, analysis and interpretation, acquisition of data and critical revision of the manuscript for important intellectual content; Rachel Saunders-Pullman study concept and design, analysis and interpretation, acquisition of data and critical revision of the manuscript for important intellectual content; Ming-X Tang PhD study concept and design, statistical analysis and support and critical revision of the manuscript for important intellectual content; Helen Mejia Santana study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content, acquisition of data; Deborah Raymond, study concept and design, acquisition of data and critical revision of the manuscript for important intellectual content; Ernest Roos acquisition of data and critical revision of the manuscript for important intellectual content; Martha Orbe-Reilly acquisition of data and critical revision of the manuscript for important intellectual content; Tanya Gurevich acquisition of data and critical revision of the manuscript for important intellectual content; Anat Bar Shira acquisition of data and critical revision of the manuscript for important intellectual content; Mali Gana Weisz acquisition of data and critical revision of the manuscript for important intellectual content; Kira Yasinovsky acquisition of data and critical revision of the manuscript for important intellectual content; Maayan Zalis acquisition of data and critical revision of the manuscript for important intellectual content; Avner Thaler acquisition of data and critical revision of the manuscript for important intellectual content; Andres Deik acquisition of data and critical revision of the manuscript for important intellectual content; Matthew James Barrett acquisition of data and critical revision of the manuscript for important intellectual content; Jose Cabassa acquisition of data and critical revision of the manuscript for important intellectual content; Mark Groves acquisition of data and critical revision of the manuscript for important intellectual content; Ann L. Hunt acquisition of data and critical revision of the manuscript for important intellectual content; Naomi Lubarr acquisition of data and critical revision of the manuscript for important intellectual content; Marta San Luciano acquisition of data and critical revision of the manuscript for important intellectual content; Joan Miravite acquisition of data and critical revision of the manuscript for important intellectual content; Christina Palmese acquisition of data and critical revision of the manuscript for important intellectual content; Rivka Sachdev acquisition of data and critical revision of the manuscript for important intellectual content; Harini Sarva acquisition of data and critical revision of the manuscript for important intellectual content; Lawrence Severt acquisition of data and critical revision of the manuscript for important intellectual content; Vicki Shanker

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Table 1

PD participants by site, mutation status and time of recruitment

	Newly screened for the AJ/ <i>LRRK2</i> consortium (n=488)		Previously genotyped (n=65)		Total (n=553)	
	<i>LRRK2</i> carriers	Non-carriers	<i>LRRK2</i> carriers	Non-carriers	<i>LRRK2</i> carriers	Non-carriers
Tel-Aviv	51 (20.5%)	198 (79.5%)	14 (60.6%)	9 (39.1%)	65 (23.9%)	207 (76.1%)
Beth-Israel	22 (20.0%)	88 (80.0%)	16 (57.1%)	12 (42.9%)	38 (27.5%)	100 (72.5%)
Columbia	24 (18.6%)	105 (81.4%)	13 (92.9%)	1 (7.1%)	37 (25.9%)	106 (74.1%)
Total	97 (19.9%)	391 (80.1%)	43 (66.2%)	22 (33.8%)	140 (25.3%)	413 (74.7%)

Table 2Demographics and disease characteristics of *LRRK2* G2019S carriers and non-carriers

	<i>LRRK2</i> carriers (n=97)	Non-carriers (n=391)	p-value
Female gender, n (%)	50 (51.5%)	148 (37.9%)	0.015 *
Age in years, (SD)	68.6 (8.8)	68.1 (10.3)	0.483
Age-at-onset, in years, (SD)	60.0 (10.0)	62.0 (10.5)	0.090
Duration in years, (SD)	8.6 (7.2)	6.1 (5.1)	>0.001
Education: n of post high school education (%)	69 (75.0%)	300 (78.3%)	0.488
First degree family history of PD ¹ (%)	34 (39.1%)	69 (20.5%)	<0.001
Lower extremity onset (%)	38 (40.0%)	73 (19.2%)	<0.001
Tremor at onset (%)	42 (43.8%)	214 (54.9%)	0.053 *
UPDRS-III score, (SD)	19.8 (12.8)	19.9 (11.3)	0.986
Dopa equivalent daily dose, mg, (SD)	443 (444)	348 (373)	0.032
PIGD phenotype ² (%)	51 (73.9%)	164 (54.3%)	0.003 *
MoCA score, (SD)	25.2 (2.9)	24.7 (3.9)	0.245
GDS score, (SD)	4.2 (3.2)	3.7 (3.4)	0.257
NMS score, (SD)	8.6 (4.8)	8.2 (4.9)	0.500
Dyskinesia ever present (%)	33 (34.4%)	77 (20.2%)	0.004 *
Sustained response for over five years ³ (%)	35 (72.9%)	58 (47.5%)	0.005 *

* Fisher exact.

¹ Family history information was available on 423 participants.² Motor phenotype was available on 371 participants³ Restricted to 222 participants with disease duration longer than 5 years

Table 3

Logistic Regression Model of the Association between G2019S Carrier Status (outcome) and PD Clinical Features¹

	Model adjusted for demographics ¹	
	OR (95% CI)	p-value
UPDRS-III score	0.99 (0.96-1.01)	0.405
Dopa equivalent daily dose (mg)	1.00 (1.00-1.00)	0.410
MoCA score	1.06 (0.98-1.14)	0.127
GDS score	1.00 (0.93-1.08)	0.878
NMS score	0.99 (0.94-1.05)	0.836
PIGD phenotype	1.89 (1.02-3.51)	0.043
Lower extremity onset by history	3.09 (1.70-5.31)	<0.001
Presence of dyskinesia	1.36 (0.73-2.55)	0.328
Persistent levodopa response over >5 years ²	2.16 (1.03-4.57)	0.042

¹ Adjusted for site, gender, age, education and disease duration

² Analyses including this variable were restricted to participants with disease duration >5 years