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Neuropsychological performance in *LRRK2* G2019S carriers with Parkinson's disease

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Abstract

Background—Ashkenazi Jewish (AJ) *LRRK2* carriers are more likely to manifest the postural instability gait difficulty (PIGD) motor phenotype than non-carriers but perform similarly to non-carriers on cognitive screening tests.

Objective—To compare the cognitive profiles of AJ with Parkinson's disease (PD) with and without *LRRK2* G2019S mutations using a comprehensive neuropsychological battery.

Methods—We administered a neuropsychological battery to PD participants in the Michael J. Fox Foundation AJ consortium. Participants (n=236) from Beth Israel Medical Center, NY, Columbia University Medical Center, NY and Tel Aviv Medical Center, Israel included 116 *LRRK2* G2019S carriers and 120 non-carriers. *Glucocerebrosidase* mutation carriers were excluded. We compared performance on each neuropsychological test between carriers and non-carriers. Participants in New York (n=112) were evaluated with the entire battery. Tel Aviv participants (n=124) were evaluated on attention, executive function and psychomotor speed tasks. The association between G2019S mutation status (predictor) and each neuropsychological test (outcome) was assessed using linear regression models adjusted for PIGD motor phenotype, site, sex, age, disease duration, education, Unified Parkinson's Disease Rating Scale (UPDRS) Part III, levodopa equivalent dose, and Geriatric Depression Score (GDS).

Results—Carriers had longer disease duration ($p<0.001$) and were more likely to manifest the PIGD phenotype ($p=0.024$). In adjusted regression models, carriers performed better than non-carriers in Stroop Word Reading ($p<0.001$), Stroop Interference ($p=0.011$) and Category Fluency ($p=0.026$).

Conclusion—In AJ-PD, G2019S mutation status is associated with better attention (Stroop Word Reading), executive function (Stroop Interference) and language (Category Fluency) after adjustment for PIGD motor phenotype.

Keywords

Parkinson; Genetics; LRRK2; neuropsychological tests

Introduction

Mutations in the Leucine-Rich Repeat Kinase 2 (*LRRK2*) are the most common known cause of autosomal dominant Parkinson Disease (PD), especially in select ethnic populations.¹ For example, the most common mutation, G2019S, is present in up to 18% of Ashkenazi Jews (AJ) with PD.¹⁻³ To date, no other pathogenic mutations in *LRRK2* have been identified in the AJ population. The clinical phenotype of *LRRK2* mutation carriers is generally considered to be similar to that of idiopathic PD, but we have shown that AJ *LRRK2* carriers are more likely to manifest the postural instability gait difficulty (PIGD) phenotype than non-carriers.⁴ Among idiopathic PD patients, PIGD phenotype is associated with cognitive impairment,⁵ but it is unknown whether this association applies to genetic cases of PD (e.g. *LRRK2*). We have previously reported that in our cohort, PIGD phenotype was associated with worse Montreal Cognitive Assessment (MoCA) performance than tremor dominant and intermediate phenotype cases among participants with idiopathic PD but not among participants who are *LRRK2* G2019S mutation carriers.⁶ In addition, *LRRK2* carriers (who are more likely to manifest the PIGD phenotype) performed similarly to non-carriers on the Mini-Mental State Examination (MMSE)⁴ and on the MoCA.⁶ In order to further assess cognitive performance among PD patients who are AJ *LRRK2* G2019S carriers and non-carriers and explore the association between mutation status, PIGD phenotype and neuropsychological performance, we evaluated 236 participants in the AJ-*LRRK2* consortium from Tel Aviv, Israel, and New York with a neuropsychological battery. Given PIGD phenotype, we hypothesized that *LRRK2* mutation carriers would perform more poorly than non-carriers on neuropsychological testing.

Methods and Participants

Participants

As previously reported, AJ-PD participants were recruited at three sites, Beth Israel Medical Center (BIMC), Columbia University Medical Center (CUMC), both in New York, and Tel-Aviv Medical Center (TLVMC), in Tel Aviv, Israel.⁶ Participants 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 a family history of PD).⁷ Participants were genotyped for *LRRK2* G2019S and glucocerebrosidase (*GBA*) mutations.⁶ Carriers of *GBA* mutations were excluded. A subset of non-carriers ($n=120$) were selected to enroll in an in-depth clinical

evaluation based on willingness and convenience of location. In the current study, G2019S carriers and non-carriers were enrolled in an in-depth clinical evaluation, which included neuropsychological and psychiatric assessments.. Participants (n= 236, including 64 from BIMC, 48 from CUMC and 124 from TLVMC) included 116 *LRRK2* G2019S carriers and 120 non-carriers. Cognitive tests administered to 66 participants from TLVMC, including 50 G2019S carriers, were previously described.⁸ Institutional review boards at all participating sites approved the protocols and all participants signed consent forms prior to participating in any research procedures.

Clinical and Neuropsychological Evaluation

The clinical evaluation included a demographic and family history interview, the Unified Parkinson Disease Rating Scale (UPDRS),⁹ the Montreal Cognitive Assessment (MoCA), the Beck Depression Inventory II (BDI II), and the Geriatric Depression Scale (GDS). Postural Instability Gait Difficulty (PIGD) phenotype was computed as previously reported^{4, 10} for 229 (of 236) participants with available UPDRS-II and UPDRS-III data. A mean score of 8 tremor items on the UPDRS was computed (self-report of tremor, chin tremor, right and left arm tremor, right and left leg tremor and right and left arm action tremor), as well as a mean score of 5 PIGD items on the UPDRS (self-report of falling, freezing and walking difficulty, and gait and postural instability on exam). A ratio between the two was then computed. PIGD was defined as ratio ≥ 1.5 .¹⁰⁻¹³

The neuropsychological battery included assessments of attention (Stroop Word Reading, Digit Span), memory (Hopkins Verbal Learning Test), executive function (Stroop Interference (raw scores)), visuospatial function (Judgment of Line Orientation), language (Category Fluency, Verbal Fluency (FAS) and psychomotor speed (Finger Tapping, dominant hand Finger Tapping, non-dominant hand)).¹⁴⁻¹⁷ Participants in TLVMC were not evaluated for memory or visuospatial function.

Statistical Analysis

Demographic information, clinical characteristics, motor phenotype (PIGD versus not PIGD, including the tremor dominant phenotype and the intermediate phenotype), UPDRS-III, MoCA, BDI-II, GDS score and neuropsychological test performance were compared between carriers and non-carriers using Fisher's exact test, chi-square tests, and Student T tests as appropriate. Linear regression models were constructed to test the association between the presence or absence of the G2019S mutation (predictor) and the MoCA and each cognitive test score (outcome), separately. Models were adjusted for recruitment-site, age, sex, years of education, duration of PD, UPDRS motor score (UPDRS-III), motor phenotype (PIGD versus not PIGD), levodopa equivalent daily dose and depression (GDS score). Analyses were performed on the entire group and repeated, stratified by recruitment sites (two New York sites versus Israel).

Results

Demographics and disease characteristics of *LRRK2* G2019S carriers and non-carriers are presented in Table 1. Carriers had longer disease duration (9.4 years versus 6.3 years,

$p<0.001$), were treated with higher levodopa equivalent daily doses (389mg/day versus 220mg/day, $p<0.001$), and were more likely to manifest the PIGD phenotype ($p=0.024$) but had similar UPDRS-III scores.

Performance on the individual neuropsychological tests is presented in Table 2. Carriers performed better than non-carriers on Stroop Word Reading and Category (animal) Fluency. In separate linear regression models adjusted for recruitment site, sex, age, education, PD duration, UPDRS-III, PIGD motor phenotype, levodopa equivalent daily dose and GDS scores, carriers performed better than non-carriers in Stroop Word Reading ($p<0.001$), Stroop Interference ($p=0.011$) and Category Fluency ($p=0.026$). Performance on the MoCA and in memory, visuospatial and psychomotor speed tasks was similar between carriers and non-carriers.

Discussion

In the current study we found that AJ PD patients who are *LRRK2* G2019S carriers perform better than non-carriers on attention and executive tasks in models adjusted for demographic and disease characteristics. As previously reported, carriers were more likely to manifest the PIGD motor phenotype, and had longer disease duration.

Our findings of better cognitive function in *LRRK2* carriers than non-carriers are surprising considering that *LRRK2* G2019S carriers in our cohort were more likely to manifest the PIGD phenotype. In previous reports on participants from this cohort⁸ and in an early-onset PD cohort⁴ we found that *LRRK2* G2019S PD cases demonstrate more gait impairment than idiopathic PD, and are more likely to manifest the PIGD phenotype. While gait disturbance and PIGD phenotype are associated with worse cognitive performance in idiopathic PD,⁵ we and others have not observed differential performance between carriers and non-carriers on basic cognitive screens, including the MMSE,¹⁸⁻²⁰ the MoCA^{6, 20} and neuropsychological batteries.²⁰⁻²⁴ Here, we found better attention and executive and language performance in carriers with PD when compared to non-carriers with PD only when all three sites were included, but found no differences in memory, visuospatial performance or processing speed. We cannot conclude whether the findings of differential performance in attention and executive functioning but not in memory and visuospatial processing are a result of a differential cognitive pattern in PD *LRRK2* G2019S carriers versus non-carriers, or because of our reduced power due to missing data from the Tel Aviv site. It remains unknown why AJ *LRRK2* carriers perform better than non-carriers in the setting of worse gait performance. FMRI studies of *LRRK2* G2019S carriers *without* PD demonstrate altered connectivity during motor and cognitive tasks despite normal performance.^{25, 26} These findings suggest underlying compensatory mechanisms that precede overt clinical signs. It is possible that these compensatory mechanisms protect mutation carriers from executive and attention dysfunction, which is often present in PD.

Cognitive impairment is among the most debilitating non-motor symptom of PD and cognitive functioning is highly variable among PD patients. Autopsies of PD patients with dementia often demonstrate diffuse Lewy body disease and/or Alzheimer's changes.²⁷ Established predictors of cognitive impairment in PD include increased severity of motor

symptoms,²⁸ PIGD phenotype⁵ (and probably more specifically, freezing of gait),²⁹ depression,²⁸ older age³⁰ and longer disease duration.³⁰ We and others have shown that a patient's genetic profile may also be associated with cognitive performance, which tends to be worse in the case of *GBA* mutations,¹⁷ and better in the case of *PARKIN* mutations.³¹ The proposed mechanism of differential cognitive performance in these cases is the abundant infiltration of Lewy bodies in the cortex in the case of *GBA*, and the lack of cortical Lewy body (or other neuropathology) in *PARKIN* mutation carriers.³² This is the first study that demonstrates better cognitive performance in attention, executive and language tests in *LRRK2* G2019S carriers compared to non-carriers. The pathology associated with better cognitive functioning among *LRRK2* carriers is unknown. Autopsies of *LRRK2* mutation carriers show marked neuropathological heterogeneity, including Lewy body pathology (restricted to brain stem structures or infiltrating the cortex), tau pathology and, rarely, concomitant Alzheimer's pathology.^{32, 33} Additional studies are required to test whether there is less cortical Lewy body involvement among *LRRK2* G2019S carriers with PD than in non-carriers to account for better cognitive performance.

The major strengths of our study are the homogenous ethnic group, the large sample size and the comprehensive neuropsychological battery employed. We were able to adjust for potential confounders by excluding all *GBA* mutation carriers (other genes linked to PD, including *SNCA*, *PARK2* and *PINK1* are very rarely present in the AJ population)³⁴ and by adjusting for disease duration, motor severity, medications, education and depression (GDS scores) in regression models. Our most significant limitation is the study's cross-sectional design, which does not allow comparison of cognitive performance longitudinally and disease progression. An additional significant limitation of our study are the missing data on memory and visuospatial performance from the Tel Aviv site, which consists of more than half of the participants in our cohort.

Given the importance of age and disease duration on cognition in PD, longitudinal follow-up is required to compare cognitive outcomes between carriers and non-carriers. The biological mechanisms that underlie the relative protection of *LRRK2* G2019S carriers from attention and executive impairment should be explored. Additional *LRRK2* G2019S autopsy collection may help clarify the neuropathological basis of cognitive performance in *LRRK2* G2019S carriers.

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Highlights

1. LRRK2-PD patients perform better than iPD on neuropsychological tests, including executive, attention and language tasks.
2. LRRK2-related PD patient perform similarly to iPD on the MoCA.
3. Ashkenazi Jewish patients with LRRK2-PD have less tremor and more gait difficulty.

Table 1

Demographic and disease characteristics of PD participants with and without LRRK2 G2019S mutation

	Non carriers (n=120)	Carriers (n=116)	p-value
Male sex (%)	76 (63.3%)	64 (55.2%)	0.233
Age, yrs (SD)	64.5 (10.8)	66.7 (10.0)	0.109
Age-at-onset, yrs (SD)	58.2 (10.8)	57.2 (10.8)	0.506
Duration, yrs (SD)	6.3 (5.4)	9.5 (6.6)	<0.001
Education, yrs (SD)	16.3 (3.3)	15.9 (3.3)	0.313
Levodopa equivalent daily dose, mg (SD)	220 (288)	389 (402)	<0.001
Total UPDRS-III score (SD)	19.5 (11.1)	21.4 (12.2)	0.219
PIGD phenotype ¹	60 (50.8%)	73 (65.8%)	0.024
GDS (SD)	3.2 (3.2)	3.7 (3.3)	0.242
BDI II (SD) ²	8.1 (7.3)	9.6 (7.0)	0.190
MoCA (SD)	25.0 (3.4)	25.4 (2.7)	0.361

UPDRS-III: Unified Parkinson's Disease Rating Scale, motor score III; PIGD: postural instability motor difficulty; GDS: Geriatric Depression Scale; BDI-II: Beck Depression Inventory-II; MoCA: Montreal Cognitive Assessment

¹ Motor phenotype was available for 129 participants; UPDRS-II (which is required for phenotype computation) was not available for five carriers and two non-carriers

² BDI-II scores were available from 165 participants including 78 carriers and 87 non-carriers

Table 2Performance of *LRRK2* G2019S mutation carriers and non-carriers on neuropsychological testing:

Test	<i>LRRK2</i> carriers		<i>LRRK2</i> Non-carriers		P value	Adjusted P value ¹
	N	Performance	N	Performance		
Attention						
Stroop Word Reading (raw scores) ² <i>Range</i>	107	92.2 (17.8) 41-135	110	86.0 (20.5) 26-140	0.019	<0.001
Digit Span <i>Range</i>	97	7.5 (1.9) 4-14	116	7.2 (1.9) 4-14	0.262	0.225
Memory³						
Hopkins Verbal Learning-Free Recall (Trials 1-3) <i>Range</i>	57	22.9 (6.0) 12-35	54	20.7 (5.6) 7-30	0.052	0.201
Hopkins Verbal Learning-Free Recall (Delayed) <i>Range</i>	57	7.3 (3.1) 0-12	53	6.3 (3.1) 0-12	0.071	0.237
Hopkins Verbal Learning-Recognition <i>Range</i>	57	10.7 (1.5) 6-12	53	10.4 (1.6) 6-12	0.426	0.390
Visuospatial Function²						
Judgment of Line Orientation Total raw score <i>Range</i>	58	12.0 (2.3) 6-16	54	11.5 (2.9) 3-16	0.380	0.388
Executive Function						
Stroop Interference raw score ² <i>Range</i>	100	28.1 (18.2) -18 - 65	107	26.9 (14.8) -7 - 64	0.590	0.011
Psychomotor Speed						
Finger Tapping, dominant hand <i>Range</i>	110	38.3 (12.1) 13.6-60.3	108	38.5 (13.1) 7.0-67.5	0.885	0.600
Finger Tapping, non-dominant hand <i>Range</i>	108	34.3 (11.8) 6.8-62.9	106	36.6 (11.7) 8.4-63.6	0.164	0.764
Verbal Fluency						
Letter (FAS) Fluency Total raw score <i>Range</i>	116	41.9 (17.0) 6-85	120	39.0 (17.5) 4-82	0.197	0.213
Category (animal) Fluency Total raw score <i>Range</i>	115	19.6 (5.9) 5-34	120	18.0 (6.5) 0-34	0.045	0.026

¹ P value is obtained from linear regression models where each cognitive test performance is the outcome and G2019S mutation status is the predictor, adjusted for recruitment site, sex, age, education, PD duration, UPDRS-III, motor phenotype, levodopa equivalent daily dose and GDS scores

² Stroop scores were missing on 29 participants including 9 color blind individuals

³ Scores on memory and visuospatial tests were available from 112 New York participants