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Cognitive Profile of *LRRK2*-related Parkinson's Disease

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Abstract

Background—There is increasing evidence that genetic factors play a role in the variability associated with cognitive performance in Parkinson's disease (PD). Mutations in the *LRRK2* gene are the most common cause of monogenic PD; however, the cognitive profile of *LRRK2*-related PD is not well-characterized.

Methods—A cohort of 1,447 PD patients enrolled in the PD Cognitive Genetics Consortium was screened for *LRRK2* mutations and completed detailed cognitive testing. Associations between mutation carrier status and cognitive test scores were assessed using linear regression models.

Results—*LRRK2* mutation carriers (n=29) demonstrated better performance on the Mini Mental State Examination (*P*=0.03) and the Letter-Number Sequencing Test (*P*=0.005). A smaller proportion of *LRRK2* carriers were demented (*P*=0.03).

Conclusions—Our cross-sectional study demonstrates better performance on certain cognitive tests, as well as lower rates of dementia in *LRRK2*-related PD. Future longitudinal studies are needed to determine whether *LRRK2* mutation carriers exhibit slower cognitive decline.

Keywords

cognition; *LRRK2*; neuropsychological tests; Parkinson disease; working memory

INTRODUCTION

Recent evidence suggests that genetic factors could play an important role in the substantial variation in the pattern of cognitive deficits seen in Parkinson's disease (PD).[1, 2] The *APOE* ε4 allele and mutations in the *GBA* gene are both associated with a higher frequency of dementia in PD yet appear to impact largely distinct cognitive domains prior to the onset of dementia.[3–7] Additional information stands to be gained by examining cognition in monogenic forms of PD because the molecular mechanisms underlying neurodegeneration are likely to be more homogenous than those involved in "idiopathic" PD.

Mutations in the leucine-rich repeat kinase 2 (*LRRK2*; OMIM #609007) gene are the most common cause of monogenic PD.[8, 9] The motor characteristics of *LRRK2*-associated PD and idiopathic PD are thought to be generally indistinguishable.[10,11] However, mixed results have been reported with respect to non-motor features, including cognition. Some studies have found that *LRRK2* mutation carriers with PD exhibit milder cognitive symptoms and more gradual cognitive decline than non-carriers with PD,[8, 12] while others have not.[13–1516–20] To help reconcile the differences reported in the literature, we compared the performance of *LRRK2* mutation carriers and non-carriers on a detailed neuropsychological assessment in a large, well-characterized multicenter PD cohort.

METHODS

Subjects

The study included 1,447 participants with PD from eight sites that comprise the PD Cognitive Genetics Consortium (PDCGC), who were screened for known *LRRK2* mutations as described previously[21] and in the e-Supplement. Participants were required to meet the United Kingdom PD Society Brain Bank clinical diagnostic criteria for PD[22] with the exception of those from UCLA who satisfied clinical diagnostic criteria for PD as described elsewhere.[23] Four participants failed genotyping and 21 subjects (all mutation non-carriers) were missing disease duration data and were thus excluded from analyses. Sixty-seven subjects (all mutation non-carriers) who did not complete greater than half of the cognitive measures were excluded from analyses involving continuous measures but not from those involving the categorical diagnostic variable (demented vs. non-demented). The institutional review board of each participating institution approved the study, and all participants provided written informed consent.

Cognitive/clinical variables

Seven cognitive tests were administered by at least seven of eight sites, including the Mini Mental State Examination (MMSE[24]) and tests measuring specific cognitive domains: *learning/memory* (Hopkins Verbal Learning Test-Revised [HVLT][25]), *attention/executive function* (Letter-Number Sequencing Test [LNST][26] and Trailmaking Parts A and B[27]), *language processing* (semantic and phonemic verbal fluency[28]), and *visuospatial abilities* (Benton Judgment of Line Orientation [JOLO][29]). Motor symptom severity (see e-Supplement) was obtained at seven of eight sites.

Cognitive data at six of the eight sites were discussed at a clinical consensus diagnosis conference, and participants were diagnosed as demented or non-demented using all available neuropsychological and clinical data at each site, as described elsewhere.[4, 30, 31] At the two remaining sites, participants were not assigned clinical cognitive diagnoses (see e-Supplement).

Statistical methods

The association between *LRRK2* mutation carrier status and clinical/cognitive variables was assessed by separate linear regression analyses, applying the generalized estimating equation to account for relatedness in the study sample. Exact logistic regression was performed to determine the association between clinically diagnosed dementia and *LRRK2* mutation status. Analyses were adjusted for age at testing, sex, site, disease duration (time since diagnosis at UCLA and time since symptom onset at all other sites), and years of education. For analyses involving Trailmaking Part B, Trailmaking Part A was also included as a covariate. Statistical tests were two-tailed; the significance threshold was set at $P < 0.05$. Given the exploratory nature of the study, no adjustments for multiple comparisons were made. Stata version 12 was used for all analyses (StataCorp, College Station, TX).

RESULTS

Twenty-nine participants with *LRRK2* mutations were identified, including two members from each of three families and three members from another family. Twenty-two were heterozygous for the G2019S mutation, two were homozygous for G2019S, and five were heterozygous for the R1441C mutation. Sample demographic, clinical, and cognitive characteristics for mutation carriers and non-carriers are shown in Table 1. Demographic and clinical data stratified by site are presented in Table e-1 (e-Supplement).

Adjusted linear regression results for cognitive test scores are presented in Table 2. *LRRK2* mutation carriers performed significantly better than non-carriers on the LNST and MMSE. The effect sizes, shown by the β coefficients, indicate the expected difference in mean LNST scores was 1.19 and in MMSE scores was 0.74, given the same values for all other covariates. Mutation carriers also had less severe motor symptoms, as assessed by the MDS-UPDRS III, than non-carriers. These associations held when the analyses were restricted to G2019S heterozygotes (Table e-2, supplement).

LRRK2 mutation carriers demonstrated a lower prevalence of dementia than non-carriers (4% vs. 19.6%). Exact logistic regression analyses that controlled for age, sex, education,

disease duration, and site demonstrated that this difference was statistically significant (Table 2).

Discussion

The current study offers evidence that mutations in the *LRRK2* gene might result in differences in cognitive phenotype in PD patients, specifically higher global cognition and lower prevalence of dementia, as well as better working memory (executive) performance when compared to non-mutation carriers. Less severe overall motor dysfunction exhibited by *LRRK2* mutation carriers in conjunction with better cognitive test performance suggests the possibility of overall milder disease in these patients, although these findings require replication.

Early descriptive studies suggested that *LRRK2* mutation carriers diagnosed with PD might show milder cognitive symptoms in comparison to non-carriers with PD,[8, 1215] while in contrast, others found no difference in MMSE scores between *LRRK2* mutation carriers and non-carriers with PD.[13, 14, 16, 19, 32] In the current study, we observed a significantly lower rate of dementia and higher mean MMSE scores in *LRRK2* mutation carriers compared with non-carriers. We also found a notable difference in the range of MMSE scores, such that *LRRK2* mutation carriers all had scores of 24 or higher in the absence of differences in mean disease duration. Similar to our findings, Estanga et al.[20] found a lower proportion of dementia cases among *LRRK2* mutation carriers compared to non-carriers, although this difference failed to reach significance. The suggestion that *LRRK2* mutations are associated with a lower likelihood of developing cognitive impairment might be explained in part by the neuropathologic features of *LRRK2*-related PD. Although widely heterogeneous,[33, 34] in a recent meta-analysis of 37 *LRRK2* mutation-positive autopsy cases with a clinical diagnosis of PD,[35] a substantial proportion (20/37, 54%) lacked Lewy body pathology and this finding was not restricted to specific *LRRK2* mutations. Further, the presence of Lewy body pathology was associated with a higher proportion of cognitive impairment (including dementia) diagnosed prior to death, while the group without Lewy body pathology displayed a predominantly motor phenotype. Given the association between Lewy body disease and more severe cognitive dysfunction in patients with PD reported by these authors and others,[36, 37] it is perhaps not surprising that *LRRK2* cohorts, which are likely enriched with Lewy body-negative cases, might exhibit overall milder cognitive symptoms.

Importantly, for the first time we demonstrate a difference between *LRRK2* mutation carriers and non-carriers with PD on a sensitive measure of working memory (an executive function). Previous studies that evaluated aspects of executive functioning found no differences in performance between *LRRK2* mutation carriers and non-carriers.[16–19] Often, however, the more frontally mediated tasks used in these studies involved motor skills or timed task performance. Here, we found a significant difference between *LRRK2* mutation carriers and non-carriers on a sensitive working memory task that does not require motor involvement and is not timed. These findings suggest that *LRRK2* mutation carrier status might be associated with less impairment on working memory, an area of cognition that is frequently impacted early in PD. This result conflicts with a recently published study[20] of *LRRK2* R1441G mutation carriers with PD that found no difference across several sensitive

cognitive measures, including LNST. However, our sample was largely composed of G2019S carriers (24/29, 83%), suggesting that specific *LRRK2* mutations might be associated with differential test performance.

Our study had some limitations. Importantly, this study is cross-sectional; only longitudinal research will provide evidence for whether the overall cognitive course differs between *LRRK2* mutation carriers and non-carriers. In addition, although we examined a large, well-defined PD cohort, our sample of *LRRK2* mutation carriers remains relatively small. Given the exploratory nature of the study, we did not correct for multiple comparisons. Finally, the pattern of performance across cognitive measures, when looking at raw scores, suggests that we might have lacked adequate power to detect statistically significant differences on several other cognitive tests.

Our findings add to a growing body of evidence which suggests that genetic factors play an important role in determining cognitive performance in PD. Given the near ubiquitous, yet heterogeneous nature of cognitive impairment in PD, identification of subgroups associated with better or worse cognitive outcomes is an important step toward tailoring appropriate interventions, and could inform inclusion for enrollment in long-term cognitive treatment and prevention trials. Future large, longitudinal investigations will be needed to reveal whether *LRRK2* mutation carrier status predicts a more stable cognitive course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and clinical data for *LRRK2* mutation carriers vs. non-carriers

	***LRRK2* Status**		***P*** [a]
	Non-Mutation Carriers [n=1326]	**Mutation Carriers [n=29]**	
Age at visit			
Mean (SD)	68.9 (9.3)	67.9 (9.6)	0.56
Range	34.8 – 94.5	50.2 – 86.9	
Sex			
N (%) female	439 (33.1%)	10 (34.5%)	0.84
Education			
Mean (SD)	15.5 (2.7)	16.3 (2.7)	0.09
Range	7 – 20	12 – 20	
Disease Duration[b]			
Mean (SD)	8.4 (5.6)	8.9 (7.0)	0.64
Range	0 – 43	1 – 32	

Abbreviation: SD = standard deviation

[a] Pairwise *P*-value using t-tests (age, education, disease duration) or Fisher's Exact Test (sex)

[b] Disease duration was based on age at diagnosis at UCLA and age at onset at all other sites

Table 2

Cognitive test scores and clinical features: *LRRK2* mutation carriers vs. non-carriers

			Scores (raw)		Standard (z-scores)		Regression Results[a]			
Cognitive Measures	**N (Total)**	**N (Mutation carriers)**	**Non-Mutation Carriers Mean (SD) Range**	**Mutation Carriers Mean (SD) Range**	**Non-Mutation Carriers Mean (SD) Range**	**Mutation Carriers Mean (SD) Range**	**Coeff.[b]**	**Std. Error**	**95% CI**	***P***
MMSE	1237	27	27.7 (2.4) 11 – 30	28.6 (1.6) 24 – 30	−1.10 (1.87) −13.84 – 0.86	−0.42 (1.32) −4.3 – 0.86	0.74	0.35	0.05, 1.42	**0.034**[c]
Fluency: Semantic	1344	28	17.2 (6.1) 0 – 37	19.9 (6.8) 7 – 35	−0.63 (1.05) −3.89 – 2.83	−0.17 (1.21) −2.34 – 2.31	1.79	1.16	−0.48, 4.05	0.122
Fluency: Phonemic	1317	28	35.6 (14.3) 2 – 93	41.4 (14.6) 12 – 69	−0.09 (1.09) −2.81 – 5.47	0.35 (1.34) −2.17 – 2.91	4.35	2.83	−1.20, 9.90	0.124
HVLT: Total Learning	1203	25	21.4 (6.3) 0 – 35	23.2 (4.8) 12 – 33	−0.82 (1.25) −5.04 – 2.25	−0.46 (0.91) −2.07 – 1.58	1.25	0.83	−0.39, 2.88	0.135
HVLT: Delayed	1201	25	6.8 (3.6) 0 – 12	7.9 (3.3) 0 – 12	−0.98 (1.59) −5.45 – 1.54	−0.49 (1.42) −4.94 – 1.30	0.77	0.48	−0.17, 1.71	0.111
HVLT: RDI	1190	25	9.3 (2.4) −2 – 12	9.6 (2.5) 2 – 12	n/a	n/a	0.13	0.39	−0.64, 0.90	0.737[d]
Judgment of Line Orientation	1149	27	11.2 (3.0) 0 – 15	11.7 (2.1) 8 – 15	0.71 (2.13) −2.45 – 3.99	0.91 (2.02) −1.22 – 3.99	0.39	0.45	−0.49, 1.28	0.386[d]
Letter Number Sequencing	1118	23	8.4 (3.1) 0 – 18	9.8 (2.3) 4 – 14	−0.06 (1.07) −3.0 – 3.0	0.49 (0.84) −1.67 – 2.0	1.19	0.43	0.35, 2.02	**0.005**
Trailmaking, Part B[e]	1123	25	143.6 (87.5) 28 – 300	99.8 (78.3) 35 – 300	−1.44 (1.94) −6.80 – 1.31	−0.55 (2.06) −6.80 – 1.04	−9.72	13.31	−35.80, 16.37	0.465[f]
Clinical Features			Non-Mutation Carriers	Mutation Carriers						
MDS-UPDRS III	1153	28	28.64 (12.9)	23.54 (9.1)	-	-	−5.17	1.58	−8.27, −2.08	**0.001**

			Scores (raw)		Standard (z-scores)		Regression Results[a]			
Cognitive Measures	**N (Total)**	**N (Mutation carriers)**	**Non-Mutation Carriers Mean (SD) Range**	**Mutation Carriers Mean (SD) Range**	**Non-Mutation Carriers Mean (SD) Range**	**Mutation Carriers Mean (SD) Range**	**Coeff.[b]**	**Std. Error**	**95% CI**	***P***
			3 – 79	3 – 43						
			Dementia N (%)							
Cognitive Status	1057	25	210 (19.9)	1 (4.0)	-	-	−1.99	-	−5.76, −0.07	**0.029**

Abbreviations: HVLT = Hopkins Verbal Learning Test-Revised, MDS-UPDRS III= Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III, MMSE = Mini Mental State Examination, RDI = Recognition Discrimination Index, SD = standard deviation

[a] Analyses involving cognitive measures adjusted for age, sex, education, site, and disease duration; Trailmaking, Part B analyses also adjusted for Trailmaking, Part A time. MDS-UPDRS analyses adjusted for age, sex, site, and disease duration. Linear regression analyses were used for continuous measures, exact logistic regression procedures were used to compare proportion of demented/nondemented participants

[b] Coeff. = beta coefficient, indicates the expected change in mean test score when carrying a *LRRK2* mutation given the same values for all adjustment covariates

[c] When cube transformed scores were used, $P = 0.05$

[d] When cube transformed scores were used, *P* values remained non-significant

[e] Lower score denotes better performance

[f] When log-transformed scores were used, *P* values remained non-significant