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Cognitive profile of LRRK2-related Parkinson's disease

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Authors
Srivatsal, S
Cholerton, B
Leverenz, JB
et al.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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

Sindhu Srivatsal, MD, MPH,[1†] Brenna Cholerton, PhD,[2,3†,] James B. Leverenz, MD,[4] Zbigniew K. Wszolek, MD,[5] Ryan J. Uitti, MD,[5] Dennis W. Dickson, MD,[5] Daniel Weintraub, MD,[6,7,8] John Q. Trojanowski, MD, PhD,[9,10] Vivianna M. Van Deerlin, MD, PhD,[9] Joseph F. Quinn, MD,[11,12] Kathryn A. Chung, MD,[11,12] Amie L. Peterson, MD,[11,12] Stewart A. Factor, DO,[13] Cathy Wood-Siverio, MS,[13] Jennifer G. Goldman, MD, MS,[14] Glenn T. Stebbins, PhD,[14] Bryan Bernard, PhD,[14] Beate Ritz, MD, PhD,[15,16,17] Rebecca Rausch, PhD,[17] Alberto J. Espay, MD,[18] Fredy J. Revilla, MD,[18] Johnna Devoto, PsyD,[18] Liana S. Rosenthal, MD,[19] Ted M. Dawson, MD, PhD,[19,20,21] Marilyn S. Albert, PhD,[19] Ignacio F. Mata, PhD,[2] Shu-Ching Hu, MD,[2,22] Kathleen S. Montine, PhD,[23] Catherine Johnson, PhD,[24] Thomas J. Montine, MD, PhD,[23] Karen L. Edwards, PhD,[24] Jing Zhang, MD, PhD,[23] and Cyrus P. Zabetian, MD, MS[2,22*]

[1]Virginia Mason Neuroscience Institute, Seattle, Washington, USA [2]Veterans Affairs Puget Sound Health Care System, Seattle, Washington, USA [3]Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, Washington, USA [4]Lou Ruvo Center for Brain Health, Neurological Institute, Cleveland Clinic, Cleveland, Ohio, USA [5]Department of Neurology, Mayo Clinic, Jacksonville, Florida, USA [6]Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania, USA [7]Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA [8]Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania, USA [9]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA [10]Institute on Aging, University of Pennsylvania, Philadelphia, Pennsylvania, USA [11]Portland Veterans Affairs Medical Center, Portland, Oregon, USA [12]Department of Neurology, Oregon Health and Science University, Portland, Oregon, USA [13]Department of Neurology, Emory University School of Medicine, Atlanta, Georgia, USA [14]Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA [15]Department of Epidemiology, School of Public Health, University of California Los Angeles, Los Angeles, California, USA [16]Department of Environmental Health Sciences, School of Public Health, University of California Los Angeles, Los Angeles, California, USA [17]Department of Neurology, School of Medicine, University of California Los Angeles, Los Angeles, California, USA [18]Department of Neurology and Rehabilitation Medicine,

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*__Correspondence to:__ Dr. Cyrus P. Zabetian, MD, MS, VA Puget Sound Health Care System, GRECC S-182, 1660 S. Columbian Way, Seattle, WA 98108, E-mail: zabetian@u.washington.edu

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[†]These two authors contributed equally to this work.

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University of Cincinnati, Cincinnati, Ohio, USA [19]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA [20]Neuroregeneration and Stem Cell Programs, Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA [21]Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA [22]Department of Neurology, University of Washington School of Medicine, Seattle, Washington, USA [23]Department of Pathology, University of Washington School of Medicine, Seattle, Washington, USA [24]Department of Epidemiology, School of Medicine, University of California Irvine, California, USA

Abstract

Background: Increasing evidence suggests 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. © 2015 International Parkinson and Movement Disorder Society

Key Words: cognition; *LRRK2*; neuropsychological tests; Parkinson's disease; working memory.

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 before 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] whereas others have not.[13-20] 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 constitute the PD Cognitive Genetics Consortium, who were screened for known *LRRK2* mutations as described previously[21] and in the Supplemental Data. 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[25]), *working memory/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[29]). Motor symptom severity (see Supplemental Data) 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 by 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 (Supplemental Data).

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 Supplemental Data Table e-1.

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 (Supplemental Data Table e-2).

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).

TABLE 1. Demographic and clinical data for *LRRK2* mutation carriers vs. non-carriers

	LRRK2 Status		
	Non-Mutation Carriers [n = 1,326]	Mutation Carriers [n = 29]	*P*[a]
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	

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.

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 with 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 with non-carriers with PD,[8,12,15] whereas 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 with 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. Furthermore, the presence of Lewy body pathology was associated

TABLE 2. Cognitive test scores and clinical features: *LRRK2* mutation carriers vs. non-carriers

			Scores (raw)		Standard (*z*-scores)		Regression Results[a]			
Cognitive Measures	(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	1,237	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	1,344	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	1,317	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	1,203	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	1,201	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	1,190	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	1,149	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	1,118	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]	1,123	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	1,153	28	28.64 (12.9) 3-79	23.54 (9.1) 3-43	—	—	−5.17	1.58	−8.27, −2.08	**0.001**
			Dementia N (%)							
Cognitive status	1,057	25	210 (19.9)	1 (4.0)	—	—	−1.99	—	−5.76, −0.07	**0.029**

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 nonsignificant
[e]Lower score denotes better performance.
[f]When log-transformed scores were used, *P* values remained nonsignificant.

with a higher proportion of cognitive impairment (including dementia) diagnosed before death, whereas 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 that 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. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Relationship of Age of Onset and Family History in Parkinson Disease

Matthew J. Barrett, MD, MSc,[1]* Nicholas E. Hac, BS,[2] Guofen Yan, PhD,[3] Madaline B. Harrison, MD,[1] and G. Frederick Wooten, MD[1]

[1]Department of Neurology, University of Virginia, Charlottesville, Virginia, USA [2]School of Medicine, University of Virginia, Charlottesville, Virginia, USA [3]Department of Public Health Sciences, University of Virginia, Charlottesville, Virginia, USA

ABSTRACT

Background: The aim of this study was to determine whether age of onset of Parkinson disease (PD) is associated with differences in PD risk and PD age of onset in parents and siblings.

Methods: Clinical and detailed family history data were available for 1,114 PD probands.

Results: Proband age of onset was not associated with differences in PD prevalence or PD age of onset in parents. Proband age of PD onset <50, compared with ≥50 years, was associated with significantly greater risk of PD in siblings (hazard ratio: 2.4; $P = 0.002$; 95% confidence interval: 1.4, 4.1), and proband age of onset was significantly correlated with sibling age of onset (Somer's D = 0.20; $P = 0.018$).

Conclusions: Proband age of PD onset is not associated with differences in parental PD risk. Siblings of PD patients with onset before age 50 are at increased risk of PD and are more likely to have early-onset disease. © 2015 International Parkinson and Movement Disorder Society

Key Words: Parkinson disease; age of onset; family history; familial aggregation; genetics

*Correspondence to: Dr. Matthew J. Barrett, Department of Neurology, University of Virginia, P.O. Box 800394, Charlottesville, VA 22908, USA; mjbarrett@virginia.edu

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One of the greatest risk factors for Parkinson disease (PD) is a positive family history.[1-3] Though many genetic causes and risk factors of PD have been discovered, identified genetic factors currently only account for approximately 20% to 30% of disease risk.[4,5] Another important risk factor for PD is advancing age. Though PD usually emerges later in life, it may occur at any time during adulthood. Previous studies reported that those with early-onset PD were more likely to have a family history of PD,[6,7] suggesting that there may be a greater genetic contribution in this group of PD patients. The aims of this study were to determine whether, in a large, clinic-based cohort, (1) earlier PD age of onset is associated with a greater likelihood of a family history of PD in parents and siblings and (2) whether probands' age of onset is associated with the age of onset of affected family members.

Patients and Methods

Between 1996 and 2010, clinical and family history data for 1,114 PD patients observed at the University of Virginia Movement Disorders Clinic (Charlottesville, VA) were collected in a clinical database. Diagnosis of PD was determined by a movement disorders specialist. Each PD patient, the proband, was queried about family history of PD in parents and siblings. For each family member, current age or age at death was recorded. For family members reported to have PD, age at symptom onset and source of diagnosis were recorded. This study was approved by the institutional review board at the University of Virginia.

Risk of Parkinson Disease

PD incidence and prevalence increase rapidly after age 50, and those with onset before 50 have previously been considered to have early onset.[8] In our population, neither probands nor family members had an age of PD onset younger than 30 years. PD risk (PD events/100 person-years) was estimated for mothers, fathers, and siblings at younger (30-50 years) and older (≥50 years) ages. PD risk at younger ages was estimated by dividing the number of family members with PD onset between ages 30 and 50 years by total time at risk. Time at risk was defined as the time in years from 30 years of age to either age of onset of PD in affected family members, current age at the time