Published in final edited form as:

Mov Disord. 2015 April 15; 30(5): 728–733. doi:10.1002/mds.26161.

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

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2. Statistical Analysis: A. Design – KLE, CJ, BC, CPZ B. Execution – CJ, BC, KLE C. Review and Critique: SS, CPZ, BC, JBL, ZKW, RJU, DWD, DW, JQT, VMV, JFQ, KAC, ALP, SAF, CWS, JGG, GTS, BB, BR, AJE, FJR, JD, LSR, TMD, MSA, IFM, S-CH, KSM, CJ, TJM, KLE, JZ
3. Manuscript Preparation: A. Writing of the first draft-SS, KSM, BC, CPZ B. Review and Critique- SS, BC, JBL, ZKW, RJU, DWD, DW, JQT, VMV, JFQ, KAC, ALP, SAF, CWS, JGG, GTS, BB, BR, AJE, FJR, JD, LSR, TMD, MSA, IFM, S-CH, KSM, CJ, TJM, KLE, JZ

Financial Disclosure/Conflict of Interest:

This research was supported by the National Institutes of Health (K23 NS060949, P50 NS062684, P50 NS053488, P50 NS038367, P50 NS038377, P50 NS072187, R01 NS065070, R01 NS057567, and U01 NS082133), the Department of Veterans Affairs (1101BX000531), the Parkinson's Disease Foundation, the Nancy and Buster Alvord Endowment, the Jane and Lee Seidman Fund, the Consolidated Anti-Aging Foundation, and gifts from Carl Edward Bolch, Jr, and Susan Bass Bolch. The funding sources did not provide scientific input for the study.

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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* $\epsilon 4$ 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.^{13–15,16–20} 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 previously²¹ and in the e-Supplement. Participants were required to meet the United Kingdom PD Society Brain Bank clinical diagnostic criteria for PD²² 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 (MMSE²⁴) and tests measuring specific cognitive domains: *learning/memory* (Hopkins Verbal Learning Test-Revised [HVLRT]²⁵), *attention/executive function* (Letter-Number Sequencing Test [LNST]²⁶ and Trailmaking Parts A and B²⁷), *language processing* (semantic and phonemic verbal fluency²⁸), 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, 12, 15} 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 study²⁰ 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.

Acknowledgments

This research was supported by the National Institutes of Health (K23 NS060949, P50 NS062684, P50 NS053488, P50 NS038367, P50 NS038377, P50 NS072187, R01 NS065070, R01 NS057567 and U01 NS082133), the Department of Veterans Affairs (1101BX000531), the Parkinson's Disease Foundation, the Nancy and Buster Alvord Endowment, the Jane and Lee Seidman Fund, the Consolidated Anti-Aging Foundation, and gifts from Carl Edward Bolch, Jr, and Susan Bass Bolch. The funding sources did not provide scientific input for the study. We thank our research subjects and family members for their participation in this study.

Author disclosures

Dr. Cholerton reports no relevant disclosures and is funded by NIH.

Dr. Srivatsal reports no relevant disclosures; she received an honorarium from APDA.

Dr. Leverenz reports consulting fees from Boehringer-Ingelheim, Piramal Healthcare, and Navidea Biopharmaceuticals and is funded by grants from the Department of Veterans Affairs, American Parkinson Disease Association, Michael J. Fox Foundation, NIH, and the Parkinson's Disease Foundation.

Dr. Wszolek receives support from the NIH/NINDS, Mayo Clinic Center for Regenerative Medicine, and the gift from Carl Edward Bolch, Jr., and Susan Bass Bolch. Mayo Clinic and Dr. Wszolek have a financial interest in technologies entitled, "Identification of Mutations in PARK8, a Locus for Familial Parkinson's Disease" and "Identification of a Novel LRRK2

Mutation, 6055G>A (G2019S), Linked to Autosomal Dominant Parkinsonism in Families from Several European Populations”. Those technologies have been licensed to commercial entities, and to date, Dr. Wszolek has received royalties <\$1.500 through Mayo Clinic in accordance with its royalty sharing policies.

Dr. Uitti serves as Associate Editor for Neurology for which he receives some personal compensation and is funded by NIH grants

Dr. Dickson reports no relevant disclosures and is funded by the NIH.

Dr. Weintraub reports consulting or advisory board membership with honoraria from Teva Pharmaceuticals, Eli Lilly and Company, Lundbeck Inc., Biogen, Pfizer, Avanir Pharmaceuticals, and Merck & Co.. Honoraria from Michael J. Fox Foundation for Parkinson’s Research, American Psychiatric Publishing, Teva Pharmaceuticals, CHDI Foundation, and Alzheimer’s Disease Cooperative Study. Intellectual property rights from licensing fees from the University of Pennsylvania. Research funding support from National Institutes of Health, Michael J. Fox Foundation, and Novartis Pharmaceuticals.

Dr. Trojanowski serves as an Associate Editor of Alzheimer’s & Dementia; may accrue revenue on patents held by the University of Pennsylvania wherein he is inventor. Modified avidin-biotin technique, Method of stabilizing microtubules to treat Alzheimer’s disease, Method of detecting abnormally phosphorylated tau, Method of screening for Alzheimer’s disease or disease associated with the accumulation of paired helical filaments, Compositions and methods for producing and using homogeneous neuronal cell transplants, Rat comprising straight filaments in its brain, Compositions and methods for producing and using homogeneous neuronal cell transplants to treat neurodegenerative disorders and brain and spinal cord injuries, Diagnostic methods for Alzheimer’s disease by detection of multiple MRNAs, Methods and compositions for determining lipid peroxidation levels in oxidant stress syndromes and diseases, Compositions and methods for producing and using homogenous neuronal cell transplants, Method of identifying, diagnosing and treating alpha-synuclein positive neurodegenerative disorders, Mutation-specific functional impairments in distinct tau isoforms of hereditary frontotemporal dementia and parkinsonism linked to chromosome-17: genotype predicts phenotype, Microtubule stabilizing therapies for neurodegenerative disorders, and Treatment of Alzheimer’s and related diseases with an antibody; and he receives research support from the NIH (AG 10124, AG 17586, AG-19724AG 024904, NS053488,AG029213 and the Marian S. Ware Alzheimer Program).

Dr. Van Deerlin reports no disclosures.

Dr. Quinn reports consulting fees from Merck and speaking fees from Novartis. Dr. Quinn is also reimbursed by Elan, Baxter, Bristol-Meyers Squibb, and Roche for the conduct of clinical trials. Dr. Quinn is also funded by grants from the NIH and Department of Veterans Affairs.

Dr. Chung reports no disclosures and is funded by a VA Merit Pilot grant.

Dr. Peterson reports no disclosures and is funded by a VA Career Development Award and by the Michael J. Fox Foundation and NIH.

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Dr. Stebbins serves as a consultant for Adamas Pharmaceuticals, Inc., Ceregene, Inc., CHDI Management, Inc., Ingenix Pharmaceutical Services (i3 Research), Neurocrine Biosciences, Inc. He receives honoraria from Movement Disorder Society, American Academy of Neurology, and Michael J. Fox Foundation for Parkinson's Research. He serves on the editorial board for the Journal of Clinical and Experimental Neuropsychology. He receives grant support from the NIH, Michael J. Fox Foundation for Parkinson's Research, and Dystonia Coalition, CHDI Management, Inc.

Dr. Bernard reports no disclosures.

Dr. Ritz reports no disclosures and is funded by grants from the NIH.

Dr. Rausch reports no disclosures and received support from NIH P50 NS038367.

Dr. Factor reports consulting fees from Ipsen Biopharmaceuticals and Merz. Grant support from Teva Neurosciences, Ipsen Biopharmaceuticals, EMD Serono, Ceregene, Michael J Fox Foundation, NIH/NHLBI (PO1 eS 016731-01 (PI Gary Miller, PhD), NIH 1 RO1 NS065070-01A1 (PI Cyrus Zabetian, MD, MSc), NINDS U01 NS052592-2CARE (PI Merit Cudkowica, MD), Royalties from UpToDate, Blackwell Futura, Demos.

Ms. Wood-Siverio reports no disclosures.

Dr. Espay is supported by the K23 career development award (NIMH, 1K23MH092735); has received grant support from CleveMed/Great Lakes Neurotechnologies, and Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member for Solvay (now Abbvie), Chelsea Therapeutics, TEVA, Impax, Merz, Pfizer, Solstice Neurosciences, Eli Lilly, and USWorldMeds; royalties from Lippincott Williams & Wilkins and Cambridge; and honoraria from Novartis, UCB, TEVA, the American Academy of Neurology, and the Movement Disorders Society. He serves as Associate Editor of Movement Disorders and Frontiers in Movement Disorders and on the editorial board of The European Neurological Journal.

Dr. Revilla is a consultant and speaker for Lundbeck Speaker's Bureau and UCB Speaker's Bureau.

Dr. Devoto is supported by the Michael J Fox Foundation.

Dr. Rosenthal reports no disclosures; she receives a lecture honorarium from the Edmund Safra Foundation.

Dr. Dawson acknowledges the Adrienne Helis Malvin and Diana Henry Helis Medical Research Foundations and their direct engagement in the continuous active conduct of medical research in conjunction with The Johns Hopkins Hospital and The Johns Hopkins University School of Medicine and the Foundation's Parkinson's Disease Programs. Funding for a portion of Dr. Dawson's research was provided by Merck KGAA. Under a licensing agreement between Merck KGAA and The Johns Hopkins University, Dr. Dawson and the University shared fees received by the University on licensing some of the reagents used in his research. Dr. Dawson also was a paid consultant to Merck KGAA. The terms of this arrangement are being managed by The Johns Hopkins University in accordance with its conflict of interest policies. His work is also supported by NIH/NINDS P50NS038377, NIH/NINDS R01NS067525, NIH/NINDS U01NS082133, NIN/NIDA P50 DA00266, the JPB Foundation and the MDSCRF 2007-MSCRFI-0420-00, 2009-MSCRFII-0125-00, MDSCRF 2013-MSCRFII-0105-00. Dr. Dawson is the Leonard and Madlyn Abramson Professor in Neurodegenerative Diseases. Dr. Dawson is chair of the Scientific Advisory Board and a member of the Board of Directors of the Bachmann Strauss Dystonia and Parkinson's Disease Foundation. Dr. Dawson is a member of Scientific Advisory Board of CurePSP. Dr. Dawson is a member of American Gene Technologies International Inc., advisory board. The terms of this arrangement are being managed by The Johns Hopkins University in accordance with its conflict of interest policies.

Dr. Albert has served on scientific advisory boards for Eli Lilly, Eisai, Genentech, Biogen and Agenebio, and has received research support from GE Healthcare.

Dr. Mata reports no disclosures and is funded by grants from the Department of Veterans Affairs, NIH, and Parkinson's Disease Foundation.

Dr. Hu reports no disclosures and is supported by the NIH.

Dr. K. Montine reports no disclosures.

Dr. Johnson reports no disclosures.

Dr. Edwards reports no disclosures and is funded by grants from the NIH.

Dr. T. Montine reports honoraria from invited scientific presentations to universities and professional societies not exceeding \$5,000 per year and is funded by grants from the NIH.

Dr. Zhang reports no disclosures.

Dr. Zabetian reports no disclosures and is funded by grants from the American Parkinson Disease Association, Department of Veterans Affairs, NIH, Northwest Collaborative Care, and Parkinson's Disease Foundation.

References

1. Aarsland D, Andersen K, Larsen JP, et al. The rate of cognitive decline in Parkinson disease. *Arch Neurol*. 2004; 61(12):1906–1911. [PubMed: 15596611]

2. Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. *Mov Disord.* 2006; 21(9):1343–1349. [PubMed: 16721732]
3. Alcalay RN, Caccappolo E, Mejia-Santana H, et al. Cognitive performance of GBA mutation carriers with early-onset PD: the CORE-PD study. *Neurology.* 2012; 78(18):1434–1440. [PubMed: 22442429]
4. Chahine LM, Qiang J, Ashbridge E, et al. Clinical and biochemical differences in patients having Parkinson disease with vs without GBA mutations. *JAMA neurology.* 2013; 70(7):852–858. [PubMed: 23699752]
5. Mata I, Leverenz J, Weintraub D, et al. Variations in APOE, but not MAPT or SNCA, predicts cognitive performance in Parkinson's disease. *JAMA neurology.* In press.
6. Pankratz N, Byder L, Halter C, et al. Presence of an APOE4 allele results in significantly earlier onset of Parkinson's disease and a higher risk with dementia. *Movement disorders: official journal of the Movement Disorder Society.* 2006; 21(1):45–49. [PubMed: 16116614]
7. Tsuang D, Leverenz JB, Lopez OL, et al. APOE epsilon4 increases risk for dementia in pure synucleinopathies. *JAMA neurology.* 2013; 70(2):223–228. [PubMed: 23407718]
8. Healy DG, Falchi M, O'Sullivan SS, et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. *Lancet neurology.* 2008; 7(7):583–590.
9. Kay DM, Zabetian CP, Factor SA, et al. Parkinson's disease and LRRK2: frequency of a common mutation in U.S. movement disorder clinics. *Movement disorders: official journal of the Movement Disorder Society.* 2006; 21(4):519–523. [PubMed: 16250030]
10. Yahalom G, Orlev Y, Cohen OS, et al. Motor progression of Parkinson's disease with the leucine-rich repeat kinase 2 G2019S mutation. *Movement disorders: official journal of the Movement Disorder Society.* 2014
11. Khan NL, Jain S, Lynch JM, et al. Mutations in the gene LRRK2 encoding dardarin (PARK8) cause familial Parkinson's disease: clinical, pathological, olfactory and functional imaging and genetic data. *Brain: a journal of neurology.* 2005; 128(Pt 12):2786–2796. [PubMed: 16272164]
12. Aasly JO, Toft M, Fernandez-Mata I, et al. Clinical features of LRRK2-associated Parkinson's disease in central Norway. *Annals of neurology.* 2005; 57(5):762–765. [PubMed: 15852371]
13. Alcalay RN, Mejia-Santana H, Tang MX, et al. Self-report of cognitive impairment and minimal state examination performance in PRKN, LRRK2, and GBA carriers with early onset Parkinson's disease. *Journal of clinical and experimental neuropsychology.* 2010; 32(7):775–779. [PubMed: 20182943]
14. Ben Sassi S, Nabli F, Hentati E, et al. Cognitive dysfunction in Tunisian LRRK2 associated Parkinson's disease. *Parkinsonism & related disorders.* 2012; 18(3):243–246. [PubMed: 22056842]
15. Lesage S, Ibanez P, Lohmann E, et al. G2019S LRRK2 mutation in French and North African families with Parkinson's disease. *Annals of neurology.* 2005; 58(5):784–787. [PubMed: 16240353]
16. Belarbi S, Hecham N, Lesage S, et al. LRRK2 G2019S mutation in Parkinson's disease: a neuropsychological and neuropsychiatric study in a large Algerian cohort. *Parkinsonism & related disorders.* 2010; 16(10):676–679. [PubMed: 20933457]
17. Goldwurm S, Zini M, Di Fonzo A, et al. LRRK2 G2019S mutation and Parkinson's disease: a clinical, neuropsychological and neuropsychiatric study in a large Italian sample. *Parkinsonism & related disorders.* 2006; 12(7):410–419. [PubMed: 16750929]
18. Lohmann E, Leclerc L, De Anna F, et al. A clinical, neuropsychological and olfactory evaluation of a large family with LRRK2 mutations. *Parkinsonism & related disorders.* 2009; 15(4):273–276. [PubMed: 18718805]
19. Shanker V, Groves M, Heiman G, et al. Mood and cognition in leucine-rich repeat kinase 2 G2019S Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society.* 2011; 26(10):1875–1880. [PubMed: 21611978]
20. Estanga A, Rodriguez-Oroz MC, Ruiz-Martinez J, et al. Cognitive dysfunction in Parkinson's disease related to the R1441G mutation in LRRK2. *Parkinsonism & related disorders.* 2014

21. Mata IF, Cosentino C, Marca V, et al. LRRK2 mutations in patients with Parkinson's disease from Peru and Uruguay. *Parkinsonism & related disorders*. 2009; 15(5):370–373. [PubMed: 18980856]
22. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry*. 1988; 51(6):745–752.
23. Kang GA, Bronstein JM, Masterman DL, Redelings M, Crum JA, Ritz B. Clinical characteristics in early Parkinson's disease in a central California population-based study. *Movement disorders: official journal of the Movement Disorder Society*. 2005; 20(9):1133–1142. [PubMed: 15954133]
24. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state" A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12(3):189–198. [PubMed: 1202204]
25. Benedict RHB, Schretlen D, Groninger L, Brandt J. The Hopkins Verbal Learning Test-Revised: Normative data and analysis of inter-form and inter-rater reliability. *The Clinical Neuropsychologist*. 1998; 12:43–55.
26. Wechsler, D. WAIIS-III® Administration and Scoring Manual. San Antonio, TX: The Psychological Corporation Harcourt Brace & Company; 1997.
27. Army Individual Test Battery: Manual of directions and scoring. Washington, DC: War Department, Adjutant General's Office; 1944.
28. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Archives of clinical neuropsychology: the official journal of the National Academy of Neuropsychologists*. 1999; 14(2):167–177. [PubMed: 14590600]
29. Benton, AL.; Sivan, AB.; Hamsher, K.; Varney, N.; Spreen, O. Contributions to Neuropsychological Assessment-A Clinical Manual. Lutz, FL: Psychological Assessment Resources; 1994.
30. Cholerton BA, Zabetian CP, Quinn JF, et al. Pacific Northwest Udall Center of excellence clinical consortium: study design and baseline cohort characteristics. *Journal of Parkinson's disease*. 2013; 3(2):205–214.
31. Goldman JG, Holden S, Bernard B, Ouyang B, Goetz CG, Stebbins GT. Defining optimal cutoff scores for cognitive impairment using Movement Disorder Society Task Force criteria for mild cognitive impairment in Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society*. 2013; 28(14):1972–1979. [PubMed: 24123267]
32. Trinh J, Amouri R, Duda JE, et al. Comparative study of Parkinson's disease and leucine-rich repeat kinase 2 p. G2019S parkinsonism. *Neurobiology of aging*. 2014; 35(5):1125–1131. [PubMed: 24355527]
33. Pouloupoulos M, Cortes E, Vonsattel JP, et al. Clinical and pathological characteristics of LRRK2 G2019S patients with PD. *Journal of molecular neuroscience: MN*. 2012; 47(1):139–143. [PubMed: 22194196]
34. Paisan-Ruiz C, Lewis PA, Singleton AB. LRRK2: cause, risk, and mechanism. *Journal of Parkinson's disease*. 2013; 3(2):85–103.
35. Kalia LV, Lang AE, Hazrati LN, et al. Clinical Correlations With Lewy Body Pathology in LRRK2-Related Parkinson Disease. *JAMA neurology*. 2014
36. Aarsland D, Perry R, Brown A, Larsen JP, Ballard C. Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. *Annals of neurology*. 2005; 58(5):773–776. [PubMed: 16240351]
37. Irwin DJ, White MT, Toledo JB, et al. Neuropathologic substrates of Parkinson disease dementia. *Annals of neurology*. 2012; 72(4):587–598. [PubMed: 23037886]

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

	<i>LRRK2</i> Status		<i>P</i> ^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

^aPairwise *P*-value using t-tests (age, education, disease duration) or Fisher's Exact Test (sex)^bDisease 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

Regression Results ^a										
Cognitive Measures			Scores (raw)				Standard (z-scores)		Regression Results ^a	
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

Cognitive Measures	Scores (raw)			Standard (z-scores)		Regression Results ^a			
	N (Total)	N (Mutation carriers)	Non-Mutation Carriers		Non-Mutation Carriers		Coeff. ^b	Std. Error	95% CI
			Mean (SD)	Range	Mean (SD)	Range			
			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