RESEARCH ARTICLE

Mood and Cognition in Leucine-Rich Repeat Kinase 2 G2019S Parkinson's Disease

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ABSTRACT: The behavioral and cognitive features of the leucine-rich repeat kinase G2019S mutation in Parkinson's disease in the Ashkenazi Jewish population are not well described; therefore, we sought to more systematically characterize these features using a semi-structured psychiatric interview and neuropsychological testing. Twenty-one Ashkenazi Jewish patients having the leucine-rich repeat kinase G2019S mutation were compared with age- and sex-matched Ashkenazi Jewish patients with Parkinson's disease without mutations. Although overall rates of affective disorders were not greater in mutation carriers, the carriers exhibited a 6-fold increased risk of premorbid affective disorders (odds ratio, 6.0; $P = .10$), as determined by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders–IV. Of interest, we identified 2 leucine-rich repeat kinase carriers with bipolar disorder; no mutation-negative subjects had this diagnosis. Performance on the Hopkins Verbal Learning Test–Revised, Judgment of Line Orientation, and Frontal Assessment Battery was consistent with previous reports and did not differ between groups. Study findings suggest a possible association between premorbid mood disorders and leucine-rich repeat kinase Parkinson's disease, warranting further evaluation. © 2011 *Movement* Disorder Society

Key Words: Parkinson's disease; leucine-rich repeat kinase 2; mood; depression; cognition

Parkinson's disease is the second most common neurodegenerative disorder,[1] and its diagnostic criteria include the hallmark motor signs of bradykinesia, rest tremor, rigidity, and postural instability.[2] In practice, the clinical presentation and course of the disease is heterogeneous, with variability in onset, progression, and severity of motor and nonmotor symptoms. The basis for this variation in Parkinson's disease phenotype is unknown but thought to be a result of environmental and genetic factors.[3–7] One of these genetic factors is the leucine-rich repeat kinase 2 (*LRRK2*) gene at the PARK8 locus.[8,9] At least 8 pathogenic *LRRK2* mutations have been identified,[10,11] and the G2019S mutation is common in certain PD populations, including Ashkenazi Jews; 10%–18% of unselected Ashkenazi PD patients and 30% of those with a PD family history are reported to harbor the mutation.[12–14]

Studies on the clinical expression of G2019S and whether it differs from idiopathic PD are conflicting. Several early studies suggested that LRRK2 PD is indistinguishable from sporadic or idiopathic PD.[15,16] An analysis of a large combined multinational cohort, however, found that patients with LRRK2 mutations had a more benign course, with a lower rate of falls, slower progression, less cognitive decline, and less olfaction loss.[17] Other studies have identified a more severe disease course, with higher UPDRS scores, more dyskinesias, higher dosages of dopaminergic medication, a greater likelihood of the postural

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Funding agencies: This project was supported by the Parkinson's Study Group, the National Parkinson's Foundation and the Michael J. Fox Foundation.
Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Received: 21 December 2010; **Revised:** 5 March 2011; **Accepted:** 15 March 2011
Published online 24 May 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23746

instability and gait difficulty phenotype, and greater cognitive impairment.[18–21]

The behavioral aspects of LRRK2 are even less well established. One Italian study[18] found a high frequency of depression, anxiety, and irritability in *LRRK2* carriers, whereas another study[22] did not find higher rates of depressive symptoms in carriers than noncarriers. In a small single-family study, unaffected carriers had similar rates of depression as noncarriers, as measured on the Beck Depression Inventory–second edition (BDI-2).[23] All these studies assessed current, rather than lifetime, psychiatric symptoms.

To more fully characterize the psychiatric and cognitive features associated with LRRK2 PD, we evaluated cognitive function and lifetime risk for mood disorders in unrelated and independently ascertained Ashkenazi Jewish PD patients with the G2019S mutation.

Patients and Methods

Patient Population

Two hundred and twenty-seven unrelated Ashkenazi Jewish (AJ) Parkinson's disease patients were consecutively screened in the outpatient setting of the Department of Neurology at Beth Israel Medical Center in New York City. All participants were evaluated by movement disorder specialists blinded to genotype and were selected after meeting stringent diagnostic criteria for idiopathic Parkinson's disease.[24] Ancestry was determined by self-description. Most patients had 4 Ashkenazi Jewish grandparents. However, 5 patients were 50% AJ and 50% non-Jewish. Two additional patients had AJ heritage only from a maternal grandparent. Patients completed questionnaires detailing medical, psychiatric, and social history. Family pedigrees were constructed, and patients were asked to detail family medical and psychiatric history. The Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr scale were completed by a movement disorder specialist blinded to genotype. Peripheral blood or ''swish-and-spit'' samples for DNA were obtained with written informed consent after clinical examination was completed.

Forty-two patients were identified as *LRRK2* G2019S mutation carriers. Two were deceased, 3 were lost to follow-up, and 6 refused further testing. Thirty-one mutation-positive patients agreed to complete further neuropsychiatric and cognitive testing; of these, 26 completed both, 3 refused the structured psychiatric interview, and 2 failed to complete neuropsychological testing. Matching every patient with the *LRRK2* G2019S mutation to an AJ nonmutation carrier was performed by an unblinded research associate using criteria of current age, sex, disease duration from symptom onset, and age at symptom onset.

Of the 31 mutation-positive patients, 3 were not included because they did not have a match: the first because of long disease duration (28 years), the second because of an early age of onset (26 years old), and the third because of late age of onset and sex (83-year-old man). Prior to analysis, it was predetermined that controls had to complete both neuropsychiatric and cognitive testing for paired analyses. Of the 28 controls identified, all initially agreed to participate in the study. One control died during the study. Six controls did not complete cognitive testing. Thus, 21 carrier–control pairs were subsequently analyzed.

Molecular Methods

DNA was extracted from white blood or buccal cells using the Purgene procedure (Gentra Systems Inc., Minneapolis, MN) and the G2019S mutation in the *LRRK2* gene was genotyped using a Taqman assay (rs34637584) according to the manufacturer's instructions (Applied Biosystems, Foster City, CA).

Clinical Testing

Cognitive Testing

A research associate trained in the administration of all study measures conducted a 30-minute testing session with each participant. Testing included the Mini–Mental State Examination,[25] the Hopkins Verbal Learning Test (Form 1; HVLT-R),[26,27] Judgment of Line Orientation test (Form V; JLO),[28] and the Frontal Assessment Battery (FAB).[29,30] In addition, patients completed the Beck Anxiety Inventory (BAI)[31] and Beck Depression Inventory (BDI-2)[32] at this session.

Psychiatric Interview

Patients were asked to participate in a phone interview with a psychiatrist who administered the mood disorders module of the Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual of Mental Disorders–IV (DSM-IV). Blinded to genotype, the psychiatrist assessed each participant for lifetime history of DSM-IV mood disorders, including: major depressive disorder (MDD), dysthymic disorder, depressive disorder not otherwise specified, mood disorder secondary to a general medical condition, and bipolar disorder.

Four categories of lifetime prevalence of mood disorders were included: (1) any mood disorder, (2) any major depressive disorder (defined as single episode or recurrent MDD), (3) recurrent MDD (defined as having more than 1 episode of depression), and (4) bipolar disorder. We analyzed recurrent MDD separately because evidence suggests it is more familial.[33] If a patient reported a mood episode, age at onset was recorded. Premorbid psychiatric disorder was defined as onset at least 5 years prior to PD motor onset.

Comorbid psychiatric disorder was defined as onset fewer than 5 years prior to PD motor onset, as the prodromal syndrome of PD is generally estimated to be 4–6 years in duration.[34–38]

Statistical Methods

Demographic data for the mutation-positive and -negative individuals were compared using chi-square and ANOVA analyses. Analyses of SCID categorical mood disorders were carried out with conditional logistic regression, whereas analyses for continuous outcomes for cognitive variables were carried out with clustered random-effects generalized least-squares regression models. For time-event variables, Cox proportional hazards stratified by matching variable was utilized. Time to premorbid mood disorder onset was defined as the number of years until mood disorder onset (if onset occurred at least 5 years prior to PD onset). Observations were censored on the last clinic visit if subjects did not have onset of any mood disorder by the time of the interview. For cognitive measures, *z* scores were generated for the HVLT-R, and cutoff scores were used for the MMSE, JLO, FAB, BDI-2, and BAI. Statistical analyses were performed using STATA statistical software.

Results

Twenty-one matched pairs were analyzed. Demographic characteristics are presented in Table 1. Conditional logistic regression showed that duration, sex, age at onset, and highest degree of education were not associated with gene status.

Results of the cognitive tests are shown in Table 2. Both groups performed well above the usual cutoffs for dementia on the Mini–Mental State Examination (MMSE). Mean MMSE scores were 29.2 for *LRRK2* carriers and 28.7 for noncarriers. Performance on trials 1–3 and delayed recall of the HVLT-R, JLO, and FAB showed no statistically significant differences between carriers and noncarriers on these measures (Table 2). There were also no statistical significant differences between group means on the BAI and BDI-2.

TABLE 1. Demographics of study population

	Mutation + (n = 21)	Mutation − (n = 21)
Sex (female)	52.4%	52.4%
Age at PD onset mean (SD, min, max)	58.7 (9.7, 43, 74)	57.8 (8.7, 41, 72)
Age at testing mean (SD, min, max)	65.7 (8.9, 48, 90)	66.4 (8.7, 48, 80)
Disease duration (y) mean (SD, min, max)	7.0 (5.4, 1, 19)	8.7 (4.3, 2, 19)
Highest education level: high school, college, graduate	35%, 20%, 45%	15%, 35%, 50%
UPDRS-2 total mean (SD)	6.4 (5.8)	8.1 (4.1)
UPDRS-3 total mean (SD)	9.5 (5.6)	11.2 (5.8)

TABLE 2. Summary of behavioral and cognitive measures

	Mutation + *z* score*	Mutation − *z* score	Coefficient (95% CI)
HVLT-R trial 1	−0.64	−0.47	−0.02 (−0.11–0.07)
HVLT-R trial 2	−0.38	−0.47	0.02 (−0.05–0.09)
HVLT-R trial 3	−0.30	−0.72	0.05 (−0.02–0.12)
HVLT-R delayed recall	−0.70	−0.85	0.02 (−0.05–0.90)
	Mean raw score (SD)	Mean raw score (SD)	
MMSE[a]	29.19 (1.40)	28.67 (1.91)	0.05 (−0.04–0.14)
JLO[a]	24.24 (4.81)	22.57 (5.66)	0.01 (−0.01–0.04)
FAB[a]	16.33 (2.52)	16.05 (2.11)	0.01 (−0.05–0.08)
BDI-2[a]	10.57 (9.80)	7.81 (3.10)	0.01 (−0.01–0.03)
BAI[a]	11.14 (8.90)	7.44 (5.30)	0.02 (−0.01–0.04)

*z Score $<$ 1 SD below the normative data mean was considered significant.
[a]Cutoffs needed for significance: JLO $\leq$ 19, FAB $\leq$ 14, MMSE $\leq$ 27, BDI-2 $\geq$ 14, BAI $\geq$ 8.

Results of lifetime and premorbid risk for mood disorders are shown in Table 3. Of note, 2 patients were diagnosed with bipolar disorder using the SCID interview; both were *LRRK2* gene carriers. Therefore, bipolar disorder was not included as a separate diagnostic category but was included as part of any mood disorder. There was a statistical trend ($P = .10$) for LRRK2+ patients to have a higher risk of premorbid any mood disorder (OR, 6.0). Other subanalyses of the SCID data did not differ significantly by gene status (Table 3) but tended to be higher for premorbid risk than for lifetime.

Discussion

Our objective was to characterize the cognitive and psychiatric features of *LRRK2* G2019S mutation

TABLE 3. Comparison of lifetime and premorbid prevalence of mood disorders in *LRRK2* carriers and noncarriers

	Lifetime risk	Premorbid risk*
Any mood disorder	1.4 (0.44–4.41)	6.0 (0.72–49.84)[a]
Any major depressive disorder	2.0 (0.37–10.92)	4.0 (0.45–35.79)
Recurrent major depressive disorder	3.0 (0.31–28.84)	3.0 (0.31–28.84)
Time to any mood disorder	2.0 (0.68–5.85)	3.5 (0.73–16.85)
Time to any major depressive disorder	2.0 (0.37–10.92)	4.0 (0.45–35.79)
Time to recurrent major depressive disorder	3.0 (0.31–28.84)	3.0 (0.31–28.84)

*Premorbid defined as onset at least 5 years prior to PD motor onset.
[a]$P = .10$.

TABLE 4. Summary of results from important previous articles addressing the cognitive and/or psychiatric phenotype of LRRK2 PD

Authors	Sample	No. of *LRRK2* G2019S cases analyzed	Cognitive measures	Behavioral measures	Authors' conclusions
Aasly et al (2005)	Outpatient PD (n = 435)	10	MMSE	Descriptions only	Low prevalence of cognitive dysfunction and dementia among LRRK2 patients; psychiatric symptoms are mild
Lesage et al (2005)	Autosomal dominant familial PD (198 probands)	21	MMSE	None	Lower MMSE scores in LRRK2 PD patients than in other autosomal dominant forms (n.s. after correcting for multiple testing)
Goldwurm et al (2006)	Outpatient PD (n = 1245)	17	MMSE, clock drawing test, Rey Auditory Verbal Learning Test, verbal fluency, Raven's Colored Progressive Matrices, FAB	NPI, HAM-D	Clinical features in carriers were those of typical IPD. but behavioral abnormalities were frequent
Healy et al (2008)	Outpatient PD (n = 899)	313	MMSE	Depression, anxiety, sleep disturbance (present, absent, not recorded)	Nonmotor symptoms generally occurred at similar frequencies, but lower risk of cognitive impairment
Pankratz et al (2008)	Familial PD, excluded if cognitive decline on MMSE or if on an antidepressant (n = 840)	34	None (exclusion criterion)	GDS	No statistically significant difference by *LRRK2* gene carrier status in depressive classification as measured by the GDS
Lohmann et al (2008)	One large French white family (n = 19)	12 unaffected carriers	MMSE, Mattis Dementia Rating Scale, FAB, Trails A/B	BDI	No differences in MMSE scores or BDI between unaffected *LRRK2* carriers (n = 12) and noncarriers (n = 8)
Alcalay et al (2010)	Early-onset PD (age at onset < 51) prescreened as MMSE > 23 (n = 699)	20	MMSE, UPDRS I (item 1)	UPDRS I, item 2 was covariate for cognitive analysis only	No difference in MMSE score between *LRRK2* carriers and noncarriers in this sample of early-onset PD prescreened for MMSE > 23

Abbreviations: BDI, Beck Depression Inventory; FAB, Frontal Assessment Battery; GDS, Geriatric Depression Scale; HAM-D, Hamilton Rating Scale for Depression; IPD, idiopathic Parkinson's disease; MMSE, Mini–Mental State Examination; NPI, Neuropsychiatric Inventory; UPDRS, Unified Parkinson's Disease Rating Scale.

carriers and broaden the definition of the LRRK2 clinical phenotype to incorporate nonmotor features. Although lifetime affective disorders overall were not increased in mutation carriers versus noncarriers, there was a trend for a greater risk of premorbid mood disorders in *LRRK2*-positive PD patients compared with gene-negative patients. This suggests a possible association between premorbid mood disorders and LRRK2 Parkinson's disease.

Depression may be a risk factor for PD; epidemiologic studies indicate that depressed patients have a 2–3 times higher risk of developing PD.[39,40] In addition, a large population-based historical cohort study of first-degree relatives (FDRs) of PD patients found an increased rate of depression in the FDRs of PD patients, regardless of the patients' individual psychiatric histories.[41,42] These studies suggest a shared genetic susceptibility to depression and PD.

The literature on mood disorders in LRRK2 PD is sparse; most reports assess the presence of mood disorders from medical records or scales that measure current psychiatric symptoms, if at all. Table 4 summarizes important previous studies that used specific measures to assess the cognitive and/or psychiatric features of LRRK2-positive G2019S PD.

A putative genetic effect could be expressed at any age; individuals may not have current psychiatric symptoms despite a significant history of depression. In addition, although some studies used symptom scales as a proxy for diagnosis, "true" diagnosis requires psychiatric interview. Thus, the SCID provides 2 advantages: (1) assessment of lifetime history and (2) full diagnosis of psychiatric disorders. In addition, the SCID better detects depression and anxiety symptoms not detected on the BDI-2 and BAI in our patients. We detected a trend toward a greater risk of premorbid mood disorders in LRRK2-positive PD patients compared with patients without mutations. Determination of whether this trend highlights a true finding requires further study with a larger sample size, which is ongoing.

The complex relationships between psychiatric disorders (premorbid, prodromal, and comorbid) and PD are not yet well understood. Mood disorders may be a phenotypic expression of the *LRRK2* G2019S gene expression, or in contrast, mood disorder susceptibility genes may modify *LRRK2* mutation penetrance. Either relationship would have profound implications for PD screening and treatment. Aside from depression, we report 2 patients who developed bipolar disorder. There were no bipolar patients in the matched noncarrier PD group. To our knowledge, this is the first report suggesting that there may be an association between bipolar disorder and the *LRRK2* gene. Further study is necessary to explore this possibility, as this observation could be solely due to chance.

There are several shortcomings of the SCID. This diagnostic interview is not used commonly in the Parkinson's literature to assess mood disorders; the interview is long and time consuming. Retrospective recollection of mood disorders could be biased by current mood state, among many other factors. The SCID is also interviewer dependent. In our study all interviews were conducted by a single experienced psychiatrist, blinded to genotype, in an attempt to eliminate variability between raters.

There were no significant differences in performance by gene status on the FAB, HVLT-R, and JLO. Our patient population scored within normal range on the MMSE. The cognitive profile detected in this study is consistent with previous literature on Parkinson's disease.[43,44] Although the MMSE results were in the normal range, the MMSE may be a poor screen for the subcortical dementia syndrome more commonly seen in Parkinson's disease.[45–48] This finding parallels the results of a recent study of early-onset LRRK2 PD patients by Alcalay et al, in which their sample had a mean MMSE score of 29.2.[49] At the time of study design, the Montreal Cognitive Assessment was not widely used or tested. Future studies may benefit by utilizing screens that are more sensitive to the cognitive deficits associated with Parkinson's disease. Because of time restrictions, the battery of tests was limited such that examinees could complete testing in 30 minutes. A more extensive battery of tests may have detected other deficits.

Despite our small sample size, this study is one of the largest to date to specifically address the psychiatric and cognitive phenotype of LRRK2 PD. These data will be further expanded in upcoming years in a multicenter effort to better characterize the features of LRRK2 PD. ■

Acknowledgments: The authors acknowledge Monica Sethi, Paul Soto, and Jeannie Soto-Valencia for their work on this project.

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