RESEARCH ARTICLE

Clustering of Motor and Nonmotor Traits in Leucine-Rich Repeat Kinase 2 G2019S Parkinson's Disease Nonparkinsonian Relatives: A Multicenter Family Study

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ABSTRACT: Objectives: The objective of this study was to determine phenotypic features that differentiate nonparkinsonian first-degree relatives of PD leucine-rich repeat kinase 2 (*LRRK2*) G2019S multiplex families, regardless of carrier status, from healthy controls because nonparkinsonian individuals in multiplex families seem to share a propensity to present neurological features.

Methods: We included nonparkinsonian first-degree relatives of *LRRK2* G2019S familial PD cases and unrelated healthy controls participating in established multiplex family *LRRK2* cohorts. Study participants underwent neurologic assessment including cognitive screening, olfaction testing, and questionnaires for daytime sleepiness, depression, and anxiety. We used a multiple logistic regression model with backward variable selection, validated with bootstrap resampling, to establish the best combination of motor and nonmotor features that differentiates nonparkinsonian first-degree relatives of *LRRK2* G2019S familial PD cases from unrelated healthy controls.

Results: We included 142 nonparkinsonian family members and 172 unrelated healthy controls. The combination of past or current symptoms of anxiety (adjusted odds ratio, 4.16; 95% confidence interval, 2.01-8.63), less daytime sleepiness (adjusted odds ratio [1 unit], 0.90; 95% confidence interval, 0.83-0.97], and worse motor UPDRS score (adjusted odds ratio [1 unit], 1.4; 95% confidence interval, 1.20-1.67) distinguished nonparkinsonian family members, regardless of *LRRK2* G2019S mutation status, from unrelated healthy controls. The model accuracy was good (area under the curve = 79.3%).

Conclusions: A set of motor and nonmotor features distinguishes first-degree relatives of *LRRK2* G2019S

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probands, regardless of mutation status, from unrelated healthy controls. Environmental or non-*LRRK2* genetic factors in *LRRK2*-associated PD may influence penetrance of the *LRRK2* G2019S mutation. The relationship of these features to actual PD risk requires longitudinal observation of *LRRK2* familial PD cohorts.

Key Words: Parkinson's disease; G2019S; LRRK2; motor UPDRS; anxiety; daytime sleepiness

The leucine-rich repeat kinase 2 (*LRRK2*) G2019S is a causative mutation for Parkinson's disease (PD) with a reduced, and variable age-related penetrance that is found in approximately 5% to 6% of familial PD cases and 1% to 2% of sporadic cases.[1] Additional non-LRRK2 genetic or environmental factors may contribute to a higher penetrance in multiplex families when compared with *bona fide* isolated PD cases.[2] In a prior case-control *LRRK2* G2019S mutation family study,[3] *LRRK2* mutation-carrying nonparkinsonian first-degree relatives of *LRRK2* G2019S PD cases were different from unrelated healthy controls on several clinical phenotypic variables and shared several of these differences with their non-mutation-carrying first-degree relatives: higher motor UPDRS (mUPDRS) scores, a higher incidence of symptoms of constipation, and worse color discrimination.[3] In another *LRRK2* family study comparing nonparkinsonian relatives and controls, olfaction was worse in nonparkinsonian relatives not carrying a *LRRK2* G2019S mutation than those with a mutation.[4] The generalizability of this finding remains to be demonstrated though, because another study did not find differences between three similar groups.[5] Overall, the clustering of motor and nonmotor signs in *LRRK2* families independent of the corresponding mutation[2] suggests that other genetic modifiers and environmental factors play a role in an increased risk for parkinsonism in these families, as recently reported for the Dynamin-3 gene.[6] The rarer event of parkinsonian phenocopies in *LRRK2* families (*LRRK2* G2019S mutation negative) is consistent with this hypothesis.[7] Examples drawn from other forms of familial forms of PD provide further support to this hypothesis: in a family with PTEN-induced kinase–associated PD, hyper-echogenicity of the substantia nigra was present in nonparkinsonian family members when compared with controls, regardless of the PTEN-induced kinase mutation status.[8]

Consequently, we postulate that the existence of more homogeneous phenotypic groups with a predisposition to neurological dysfunction in nonparkinsonian family members of *LRRK2* G2019S mutation multiplex families may help in the discovery of genetic or environmental factors that put *LRRK2* G2019S mutation carriers in these families at risk of PD. As a first step, we identified motor and nonmotor features in nonparkinsonian patients belonging to *LRRK2* G2019S mutation multiplex families using a large sample of unrelated healthy participants as controls.

Methods

Study Design

This was a secondary analysis of a multicenter cross-sectional family study. Participating centers were (1) Toronto Western Hospital Movement Disorders Centre, Toronto, Canada; (2) the Parkinson's Institute and Clinical Center, Sunnyvale, California, USA; (3) the Institute of Neurogenetics, Lübeck, Germany; and (4) the Parkinson's Disease and Movement Disorders Unit, Hospital Clinic de Barcelona, Spain.

Population

The participants were part of 2 previously reported *LRRK2* cohorts with data collected between 2006 and 2009[3] and 2011 to 2015, respectively.[9] Both original *LRRK2* cohorts had ethics committee approval.

For the present study, we included (1) nonparkinsonian, first-degree relatives of *LRRK2*-associated PD cases, with and without *LRRK2* G2019S mutations, and (2) nonparkinsonian unrelated controls defined as individuals without a neurologic disease recruited among nonblood relatives of the patients with idiopathic PD and volunteers identified through advertisements in study centers (Lübeck, Germany; Toronto, Canada; Barcelona, Spain).

Analysis

We selected *a priori* nonmotor and motor features considered to be early motor symptoms of PD and/or prodromal nonmotor features. Variables related to motor phenotype were the total score of the "old" mUPDRS[10] (continuous factor), item 4 on the postural/action upper extremity tremor, and the following items of the UPDRS part II related to motor performance: difficulty with handwriting (item 8), difficulty turning in bed (item 12), and difficulty with walking (item 15). These items were treated as binary variables: absence (score 0) versus presence (score 1-4). The variables associated with nonmotor features were individual questions about prior or current symptoms of depression, anxiety, or constipation, and the item of intellectual impairment (item 1) of

TABLE 1. Demographic and clinical variables of nonparkinsonian individuals in multiplex families with *LRRK2* G2019S Parkinson's disease cases (n = 142) and unrelated healthy controls (n = 172)

	G2019S mutation carriers, n = 52	G2019S mutation noncarriers, n = 90	*P* value[a]	Nonparkinsonian *LRRK2* family members, n = 142	Unrelated healthy controls, n = 172	*P* value[b]
Age at evaluation, y, mean (SD)	49.2 (14.5) m = 0	47.9 (12.5) m = 0	.592	48.7 (14.1) m = 0	57.1 (12.4) m = 0	<.001
Gender, M:F	28:24	39:51	.228	67:75	83:89	.85
Difficulty with handwriting (item 8, UPDRS), n (%)	0 (0.0) m = 1	3 (3.3) m = 0	>.05	3 (2.1)	6 (3.5)	.478
Difficulty in turning in bed (item 12, UPDRS), n (%)	2 (3.8) m = 0	1 (1.1) m = 0	.305	3 (2.1)	5 (2.9)	.658
Difficulty with walking (item 15, UPDRS), n (%)	1 (1.9) m = 0	3 (3.3) m = 0	.629	4 (2.8)	1 (0.6)	.154
mUPDRS (0-108), mean (SD)	1.7 (2.8) m = 1	1.8 (3.1) m = 0	.797	1.8 (2.8) m = 1	0.9 (1.6) m = 1	.001
Postural/action tremor (item 4, mUPDRS) > 0, n (%)	8 (15.4) m = 0	6 (6.7) m = 0	.102	14 (9.9)	24 (13.9)	.27
Current cognitive problems (item 1, UPDRS), n (%)	7 (13.4) m = 0	9 (10.0) m = 0	.531	16 (11.3)	38 (22.1)	.013
MMSE score (0-30), mean (SD)	29.1 (1.2) m = 0	29.2 (1.3) m = 0	.551	29.2 (1.2) m = 0	29.3 (0.9) m = 9	.432
Current or prior symptoms of depression, n (%)	20 (38.5) m = 0	25 (27.8) m = 0	.189	45 (31.7)	45 (26.6)	.327
BDI-II (0-63), mean (SD)	5.4 (5.3) m = 2	4.5 (5.7) m = 4	.365	4.8 (5.5) m = 6	4.9 (5.1) m = 9	.897
Current or prior symptoms of anxiety, n (%)	20 (39.2) m = 1	29 (32.2) m = 0	.403	49 (34.7)	14 (8.7)	<.001
Anxiety severity (standardized scores), mean (SD)	0.032 (0.8) m = 0	0.031 (0.8) m = 0	.628	0.007 (0.8) m = 0	−0.02 (0.9) m = 0	.763
Current or prior symptoms of constipation, n (%)	7 (13.7) m = 1	17 (19.1) m = 1	.419	24 (17.1)	14 (8.6)	.028
ESS score (0-24), mean (SD)	4.6 (3.3) m = 2	6.3 (3.7) m = 13	.090	4.6 (3.3) m = 2	6.3 (3.7) m = 13	<.001
B-SIT score (0-12), mean (SD)	9.8 (1.5) m = 0	9.7 (1.7) m = 0	.295	9.7 (1.6) m = 2	9.6 (1.9) m = 0	.885

LRRK2, leucine-rich repeat kinase 2; mUPDRS, part III of the Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; BDI-II, Beck Depression Inventory-I; ESS, Epworth Sleepiness Scale; B-SIT, Brief Smell Identification Test; SD, standard deviation; M, male; F, female; m, missing.
[a]G2019S mutation carriers versus G2019S mutation noncarriers.
[b]Nonparkinsonian *LRRK2* family members versus unrelated healthy controls.

the UPDRS part I collected as binary variables (presence vs absence). We considered as continuous variables the MMSE, the Beck Depression Inventory-II, State-Trait Anxiety Inventory form Y, Epworth Sleepiness Scale, and the Brief Smell Identification Test. The Barcelona cohort used the MoCA, the University of Pennsylvania Smell Identification Test, and the Hospital Anxiety and Depression Scale-Anxiety scale. The MoCA and University of Pennsylvania Smell Identification Test scores were converted to MMSE and Brief Smell Identification Test scores, respectively, using published algorithms.[11,12] When the "new" MDS-UPDRS[13] was used, the scores were converted to the "old" mUPDRS[10] as described before in one of the original cohorts.[3] We used score standardization to statistical distribution for the State-Trait Anxiety Inventory and Hospital Anxiety and Depression Scale-Anxiety scale scores.

Statistical Analyses

Univariate Analyses. Using a logistic regression model, we tested the association of each of the variables described previously with membership to nonparkinsonian relative *LRRK2* G2019S familial cases versus an unrelated healthy control group.

Multivariate Analysis and Variable Selection. Variables meeting the threshold of $P \leq .25$ after univariate analyses were included in an initial model. We used a backward variable selection method to obtain the final model, excluding independent variables with an associated $P > .1$. Age and gender were forced into the model, as biological confounders. Model validation was done using bootstrap resampling (500 replications) to test the stability of estimates.[14] The model results were presented as odds ratio and corresponding 95% confidence intervals. All analyses were performed using Stata/IC 14 (StataCorp, College Station, Texas).

TABLE 2. Final model of the combination of motor and nonmotor features that best identifies members of a leucine-rich repeat kinase 2 G2019S mutation multiplex family in nonparkinsonian individuals

Predictor	Adjusted OR (95% CI)	Test statistic, Z value	*P* value
Age at evaluation (1-year increment)	0.94 (0.92-0.96)	−5.21	<.0001
Gender (female vs male)	0.94 (0.54-1.62)	−0.24	.814
ESS score (1-unit increment)	0.90 (0.83-0.97)	−2.74	.006
Presence of past or current symptoms of anxiety (presence vs absence)	4.16 (2.01-8.63)	3.83	<.0001
mUPDRS (1-unit increment)	1.41 (1.20-1.67)	4.07	<.0001

We used a multiple logistic regression model followed by backward variable selection. ESS, Epworth Sleepiness Scale; mUPDRS, motor section of the Unified Parkinson's Disease Rating Scale. Hosmer-Lemeshow test: $P > .413$.

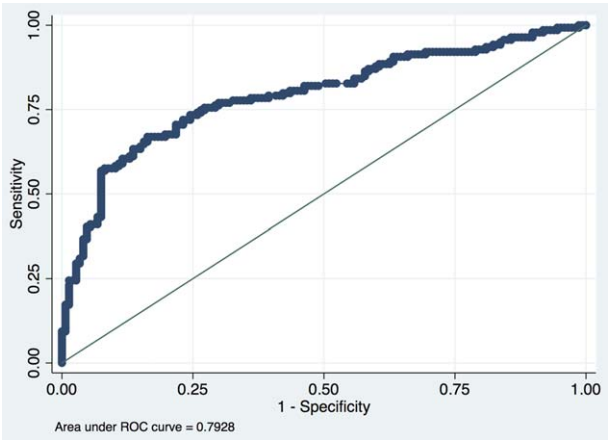

FIG. 1. Receiver operating characteristic curve of the combination of motor and nonmotor features that best distinguishes nonparkinsonian first-degree relatives of leucine-rich repeat kinase 2 G2019S-associated PD cases from unrelated healthy controls. Area under the curve = 79.3%. [Color figure can be viewed at wileyonlinelibrary.com]

Results

We included 142 *LRRK2* first-degree relatives and 172 unrelated healthy controls, all nonparkinsonian. Among the *LRRK2* G2019S mutation family members there was no difference between mutation carriers and noncarriers for the variables considered (Table 1). In an unadjusted univariate comparison, the group of nonparkinsonian first-degree relatives (regardless of a *LRRK2* G2019S mutation status) had higher mUPDRS scores, (mean [standard deviation, SD]: 1.8 [2.8] vs 0.9 [1.6]; $P = .001$), less daytime sleepiness (Epworth Sleepiness Scale scores, mean [SD]: 4.6 [3.3] vs 6.3 [3.7]; $P < .001$), more frequently reported symptoms of anxiety (34.7% vs 8.7%; $P < .001$), constipation (17.1% vs 8.6%; $P = .028$), and less frequently reported cognitive concerns when compared with unrelated healthy controls (Table 1). The *LRRK2* G2019S mutation family members (mean age [SD]: 48.7 [14.1]) were younger than unrelated healthy controls (mean age [SD]: 57.1 [12.4]; $P < .001$).

Identifying Membership to a *LRRK2* G2019S Mutation Family in Nonparkinsonian Patients by a Combination of Motor and Nonmotor features (Table 2)

The combination of the presence of past or current symptoms of anxiety (adjusted odds ratio [OR], 4.16; 95% confidence interval [CI], 2.01-8.63), less daytime sleepiness (Epworth Sleepiness Scale score, adjusted OR [1 unit], 0.90; 95% CI, 0.83-0.97), and higher mUPDRS score (adjusted OR [1 unit], 1.4; 95% CI, 1.20-1.67] best distinguished nonparkinsonian members of *LRRK2* G2019S PD multiplex families from unrelated healthy controls. After bootstrap resampling, the model estimates remained statistically significant (Supplemental Table 1). The area under the curve of the receiver operating characteristic (ROC) curve for the model was 79.3% (see Fig. 1). In addition, the model estimates were similar if we excluded *LRRK2* G2019S mutation carriers from the model (Table 3) or after frequency matching for age (Supplemental Table 2).

Discussion

The present study provides additional evidence[3] that nonparkinsonian members of *LRRK2* G2019S PD multiplex families share a set of clinical features independent of the G2019S mutation status. Using a large sample, we show the combined value of a set of motor and nonmotor features (presence of symptoms of anxiety, less daytime sleepiness, and a higher mUPDRS score), as opposed to individual features, to differentiate nonparkinsonian first-degree relatives of *LRRK2* G2019S PD cases and unrelated healthy controls. In addition, we document that this phenotypic profile is not different in nonparkinsonian *LRRK2* G2019S mutation carriers when compared with relatives who do not carry a *LRRK2* mutation. Although other *LRRK2* G2019S family studies report differentiating features between nonparkinsonian relatives depending on *LRRK2* G2019S mutation carrier status,[9,15] results have been conflicting with one study finding differences

TABLE 3. Subgroup analyses for noncarriers of the leucine-rich repeat kinase 2 (*LRRK2*) G2019S mutation for the initial model comparing nonparkinsonian members of a *LRRK2* G2019S mutation multiplex family (regardless of *LRRK2* G2019S mutation status) and unrelated healthy controls

Predictor	Adjusted OR (95% CI)	Test statistic, Z value	*P* value
Age at evaluation (1-year increment)	0.94 (0.92-0.97)	−4.25	<.0001
Gender (female vs male)	1.03 (0.56-1.88)	0.10	.919
ESS score (1-unit increment)	0.92 (0.85-1.00)	−1.81	.07
Presence of past or current symptoms of anxiety (presence vs absence)	3.56 (1.61-7.87)	3.14	.002
mUPDRS (1-unit increment)	1.37 (1.15-1.64)	3.58	<.0001

ESS, Epworth Sleepiness Scale; mUPDRS, motor section of the Unified Parkinson's Disease Rating Scale.

in motor features,[9,15] whereas another study reporting only a difference in nonmotor symptoms.[9,15] Contrary to these studies, we included an unrelated healthy control group. In addition, our study with a multicenter design increases the confidence that these results are not just specific to a certain region.

As a limitation to this study, we cannot exclude a volunteer bias if family members with subtle neurological symptoms were more interested in participating in the study; however, the unrelated controls may also be susceptible to this form of bias. The *LRRK2* G2019S mutation family relatives were younger than unrelated healthy controls, which could be a confounder. For example, the differences found in excessive daytime sleepiness could be smaller, and the differences found in the mUPDRS could be larger. The sensitivity analyses conducted with frequency matching for age further strengthens the interpretation that the current results are likely explained by membership to a *LRRK2* family, and not by age. There may also be a measurement bias for physician-rated scales such as the mUPDRS related to the knowledge of membership to a *LRRK2* family in the observed nonparkinsonian group because assessments were not blinded to membership of participants in study families. The use of methods of quantitative motor assessment could provide a more sensitive and less biased approach to further assess the meaning of the observed differences in parkinsonism-related items.[16] The absence of blinding to family membership could have been associated with a greater valuation of "soft" signs observed on the neurological examination in members of *LRRK2* families and with undervaluation in unrelated healthy controls. However, patient-reported outcome variables such as a history of anxiety and daytime sleepiness should be less susceptible to this type of bias.

More homogeneous phenotypic groups of nonparkinsonian relatives can be used in future studies to identify relevant gene–gene and gene–environmental interactions (epigenetics), addressing the following 2 fundamental questions: (1) To what extent are the observed set of features a manifestation of a network of genes, environmental factors, or the interaction of both that predispose to neurological dysfunction? 2) To what extent is this cluster of features ultimately associated with a higher risk of incident PD? Previous findings support the relevance of these questions. For example, the lifetime penetrance of *LRRK2* mutations in relatives of multiplex PD families[2] is greater than that reported in mutation carriers relatives of sporadic *LRRK2* PD cases[17]; this emphasizes the role of additional susceptibility factors besides the *LRRK2* G2019S mutation carrier status for an increased risk of PD in multiplex families. Various studies[2,18-21] have shown that other known PD-associated genetic factors can be associated with an increased penetrance of *LRRK2* mutations and modification of age at onset of PD.

A longitudinal follow-up of the nonparkinsonian individuals considered in the present study could provide information on the risk of PD in family members presenting with the identified phenotypic profile. In fact, if a phenotypic profile (possibly combined with valid biomarkers in the future) is found to be associated with increased penetrance of the G2019S *LRRK2* mutation, this may help to set inclusion criteria for G2019S *LRRK2* mutation carriers taking part in clinical trials of future preventive therapies targeting *LRRK2*-associated PD. In addition, the comparison of nonparkinsonian members of *LRRK2* G2019S PD multiplex families with relatives of sporadic *LRRK2* G2019S PD cases, or between *LRRK2* G2019S PD multiplex families with a documented high and low penetrance, may provide additional insights into how specific our findings are to families with a higher penetrance of the G2019S *LRRK2* mutation. Finally, although we have studied *LRRK2* G2019S multiplex families, it is possible that these results may generalize to other forms of familial PD. ■

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Supporting Data

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