Movement Disorders

RESEARCH ARTICLE

CLINICAL PRACTICE

Official Japanese Version of the International Parkinson and Movement Disorder Society–Unified Parkinson's Disease Rating Scale: Validation Against the Original English Version

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Abstract: The International Parkinson and Movement Disorder Society (MDS)-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) has been developed and is now available in English. Part of the overall program includes the establishment of official non-English translations of the MDS-UPDRS. We present the process for completing the official Japanese translation of the MDS-UPDRS with clinimetric testing results. In this trial, the MDS-UPDRS was translated into Japanese, underwent cognitive pretesting, and the translation was modified after taking the results into account. The final translation was approved as the Official Working Draft of the MDS-UPDRS Japanese version and tested in 365 native-Japanese–speaking patients with PD. Confirmatory analyses were used to determine whether the factor structure for the English-language MDS-UPDRS could be confirmed in data collected using the Official Working Draft of the Japanese translation. As a secondary analysis, we used exploratory factor analyses to examine the underlying factor structure without the constraint of a prespecified factor organization. Confirmatory factor analysis revealed that Comparative Fit Index for all parts of the MDS-UPDRS exceeded the minimal standard of 0.90, relative to the English version, and therefore the Japanese translation met the prespecified criterion to be designated, called an official MDS translation. Secondary analyses revealed some differences between the English-language MDS-UPDRS and the Japanese translation; however, these differences were considered to be within an acceptable range. The Japanese version of the MDS-UPDRS met the criterion as an Official MDS Translation and is now available for use (www.movementdisorders.org).

The UPDRS has been widely used since the 1980s as a standard clinical rating scale for Parkinson's disease (PD).[1,2] However, increasing evidence indicates that several symptoms frequently experienced by PD patients that affect their quality of life, such as sleep problems, sensory disturbance, urinary problems, constipation, and fatigue, are not adequately evaluated in the original

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[a]Members of the MDS-UPDRS Japanese Validation Study Group are listed in the Appendix.

Relevant disclosures and conflicts of interest are listed at the end of this article.

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UPDRS.[3] In 2001, the International Parkinson and Movement Disorder Society (MDS) sponsored a critique of the UPDRS and subsequently developed a new version of the scale, termed the MDS-sponsored UPDRS revision. This new version, the MDS-UPDRS, was intended to be less ambiguous than its predecessor as well as to incorporate a number of clinically pertinent PD-related problems poorly captured in the original version.[4] In 2008, the MDS-UPDRS successfully passed clinimetric testing with high internal consistency and reliable factor structures for each part of the scale.[4] The new MDS-UPDRS comprises four parts: Part I evaluates nonmotor experiences of daily living, Part II evaluates motor experiences of daily living, Part III evaluates motor function, and Part IV evaluates motor fluctuations and dyskinesia.

After publication of the MDS-UPDRS, the MDS set forth a specific program to designate successful translations of non-English-language versions as official MDS translations. For this purpose, the MDS has set a strict protocol and criteria for testing. Currently, several official translations (Italian,[5] Spanish,[6] French, Estonian, German, and Slovakian) have already been established, and several other language programs are in progress. Herein, we present the scale translation and clinimetric testing results of the Japanese version of the MDS-UPDRS.

Patients and Methods

Translation of the MDS-UPDRS

The MDS-UPDRS was translated into Japanese by a team of natural Japanese speakers fluent in English who belong to the Department of Neurology of Wakayama Medical University in Japan, led by Kondo. The resultant Japanese translation was further reviewed by a team led by Mizuno from the Movement Disorder Society of Japan to establish the original Japanese translation of the MDS-UPDRS. The translation was then back-translated by a team of colleagues fluent in English and Japanese who had not been involved in the original forward translation. The back-translation was reviewed by the administrative team in charge of the overall translation program (Stebbins, Goetz, LaPelle, and Tilley).

Cognitive Pretesting

Cognitive pretesting is a qualitative approach to assess instrument completion in terms of task difficulty for examiner and respondent as well as respondent interest, attention span, discomfort, and comprehension.[7] Where there were observed differences between the back-translated Japanese and English versions, items were selected for cognitive pretesting, along with questions that had been identified during cognitive pretesting of the English version. Cognitive pretesting was performed on the following sections: Part I Hallucinations and Psychosis; Features of Dopamine Dysregulation Syndrome; and Urinary Problems; Part II Freezing; Part III Postural Stability; and Rest Tremor Amplitude; Part IV Time Spent with Dyskinesia; and Functional Impact of Dyskinesia. Three experienced Japanese movement disorder specialists not involved in the original translation performed cognitive pretesting. Based on the results of the initial cognitive pretesting, additional round(s) of translation, back-translation, and cognitive pretesting could be required. After taking the cognitive pretesting results into account, the final Japanese translation was obtained.

Testing of the Japanese Version of the MDS-UPDRS

A total of 30 experienced Japanese movement disorder specialists were recruited as members of the MDS-UPDRS Japanese version validation team led by Kashihara (members are listed in the Appendix) to examine native-Japanese–speaking PD patients who had provided informed consent. The sample size for the translation study was based on the need for 5 participants per questionnaire item in order to perform the statistical analysis.[8] There are 65 items on the MDS-UPDRS: Thus, a sample of at least 325 was required. Any participants with missing values within a part were excluded from the analysis of that part only. Hence, the sample size could vary by part. The investigators obtained approval to collect the data in accord with relevant institutional ethics policies regarding human subjects. Anonymized patient data were transferred to the analysis team by a secure website. The protocol for validation of the MDS-UPDRS Japanese version was approved by the ethics committees of each institute. Informed consent was obtained from all participants before the study.

Data Analysis

Factor Analysis

M-plus (version 6.11)[9] was used to perform confirmatory and exploratory factor analyses (EFA), because the variables are categorical. We used a weighted least squares with mean- and variance-adjusted weighted least square (WLSMV) approach to factor estimation that minimizes the sum of squared differences between observed and estimated correlation matrices not counting diagonal elements. To assist in interpretation of the factors, we used an orthogonal CF-varimax rotation that constrains the factors to be uncorrelated. These methods were chosen to follow those used in the original examination of the English MDS-UPDRS.[4]

Primary Analysis

We conducted a confirmatory factor analysis (CFA)[10] as the primary analysis of the Japanese data to determine whether the factor structure for the English-language MDS-UPDRS[4] could be confirmed in data collected by using the Japanese translation. This was the primary question of interest. The CFA was conducted separately for the MDS-UPDRS Parts I to IV, with the Japanese data constrained to fall into the factors defined in the English-language data.[4] We evaluated the CFA results based on the comparative fit index (CFI). According to

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protocol, to establish a successful translation and earn the designation of "official MDS-UPDRS translation," the CFI for each part (I–IV) of the translated instrument must be 0.90 or greater, relative to the English-language version.[4] Root mean square error of approximation (RMSEA) was also calculated as another test of model fit. RMSEA values <0.05 were considered to be a good fit, and RMSEA values of 0.1 or more were considered to be a poor fit. WLSMV estimators were used to confirm a model fit.

Secondary Analysis

As a secondary analysis, we conducted an exploratory factor analysis[11] for Parts I to IV of the Japanese version of the MDS-UPDRS to explore the underlying factor structure without the constraints of a prespecified factor structure. We used a Scree plot to choose the number of factors to retain for each part. The subjective Scree test[12] is scatter plot of eigenvalues plotted against their ranks with respect to magnitude to extract as many factors as there are eigenvalues that fall before the last large drop (i.e., an "elbow" shape) in the plot. Once the factors were chosen, an item was retained in a factor if the factor loading for the item was 0.40 or greater.

The default estimator for factor analysis in M-plus is unweighted least squares (ULS). When ULS converges, it yields more-accurate parameter estimates and standard errors than does WLSMV. However, WLSMV generally outperforms ULS in convergence rates. Thus, Forero et al.[13] suggest the use of ULS. In the case of nonconvergence, however, they suggest using WLSMV, because this method might converge when ULS does not. In this case, whereas the ULS algorithm did converge, it converged to an incorrect value (i.e., a percent of variance explained that was greater than 1.0), so WLSMV was used.

The chi-square test was used to analyze, additionally, the differences in the distribution of responses for each item of the MDS-UPDRS between PD patients of Japanese and English groups.

Results

Cognitive Pretesting

A total of 12 patients with PD and their examiners were interviewed using a structured interview format typical in cognitive pretesting. During the first round of cognitive pretesting, minor word changes were suggested for features of dopamine dysregulation syndrome, urinary problems, and time spent with dyskinesia. In response to comments from patients and caregivers, we enlarged the size of characters used in questions from Part IB and Part II. No items were identified as problematic during a second round of cognitive pretesting conducted with 10 patients with PD. The modified version of the scale was approved as the Official Working Draft of the Japanese MDS-UPDRS for testing in a larger group of patients with PD.

Data Analysis

Demographics

Participants' demographic characteristics are shown in Table 1. The Japanese data set included 365 native-Japanese–speaking patients with PD who were examined using the MDS-UPDRS. In the Japanese sample, there was a greater proportion of female patients, compared to the English sample. The two cohorts were similar on age and duration of disease, but the distribution of H & Y stages were significantly different between the two cohorts ($P < 0.0005$; Table 1).

Primary Analysis: CFA

Table 2 displays the CFA models for each part of the MDS-UPDRS. For all four parts of the Japanese version, the CFI was 0.93 or greater, in comparison to the English-language factor structure. Our prespecified criterion was a CFI of 0.90 or greater; thus, we conclude that the English factor structure was confirmed in the Japanese data set.

Secondary Analysis: EFA

The factor structure of the EFA for the English version has been used as the basis for all CFAs, but our EFA of the Japanese

TABLE 1 Demographics of Japanese patients with PD in comparison with the MDS-UPDRS (English version) data

	English	Japanese	*P* Value
Total N	876	365	ns
% male	63.2	45.2	<0.0005
Age (mean ± SD)	68.2 ± 10.8	69.0 ± 9.2	ns
Disease duration (mean years ± SD)	8.3 ± 6.7	7.8 ± 6.1	ns
Years of education	NA	12.6 ± 2.7	ns
H & Y stage			<0.0005
0	0	2	
1	63	28	
2	467	164	
3	174	116	
4	109	42	
5	53	11	

SD, standard deviation; NA, not available; ns, not significant.

TABLE 2 Confirmatory factor analysis model fit

Part I: Nonmotor aspects of experiences of daily living (a two-factor model)[a]	
Japanese	CFI = 0.93; RMSEA = 0.09 (351 patients)
English language	CFI = 0.97; RMSEA = 0.05 (849 patients)
Part II: Motor aspects of experiences of daily living (a three-factor model)	
Japanese	CFI = 0.99; RMSEA = 0.07 (356 patients)
English language	CFI = 0.99; RMSEA = 0.05 (851 patients)
Part III: Motor examination (a seven-factor model)	
Japanese	CFI = 0.94; RMSEA = 0.08 (336 patients)
English language	CFI = 0.95; RMSEA = 0.08 (801 patients)
Part IV: Motor complications (a two-factor model)	
Japanese	CFI = 1.00; RMSEA = 0.06 (350 patients)
English language	CFI = 1.00; RMSEA = 0.00 (848 patients)

[a]Dopamine dysregulation syndrome was not included in this analysis because it did not load on any factor in the U.S. version.

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data set differs from that of the English-language data set in some aspects. The results of the EFA for the English and Japanese versions are shown in Table 3, including the number of factors and their associated eigenvalues and percent variance.

The Scree plots were used to determine the number of factors to be retained from the EFA. Comparison between the Scree plots for the English and Japanese cohorts revealed similarities in shape of the plots (Fig. 1), but differences were noted in the relationship between factors and their eigenvalues and percent of variance (Table 3): For Part I: Nonmotor aspects of experiences of daily living, we extracted two factors; for Part II: Motor aspects of experiences of daily living, we extracted three components; for Part III: Motor examination, we extracted seven factors; and for Part IV: Motor complications, we extracted two factors.

Chi-square (χ^2) test (Table 4) revealed greater distribution of less-severe scores on the cognitive impairment items (Part I: item 1.1) in the Japanese group, compared to the English group ($\chi^2 = 23.457$; df = 4; $P = 0.0001$). There was no significant difference of the distribution of scores on the hallucinations and psychosis item (Part I: item 1.2) ($\chi^2 = 5.962$; df = 4; not significant). In many other items, PD patients in the English group showed greater distribution of more-severe scores, including depressed mood, pain and other sensations, lightheadedness on standing, fatigue, and sleep problems in Part I; speech, saliva and drooling, doing hobbies and other activities, tremor, and getting out of bed in Part II; speech, facial expression, rigidity, finger tapping, hand movements, pronation supination, toe tapping, leg agility, and tremor in Part III; and time spent with dyskinesia, functional impact of dyskinesias, time spent in the OFF state, complexity of motor fluctuations, and painful OFF-state dystonia in Part IV. Japanese PD patients showed greater distribution in more-severe scores than English groups in items constipation problems in Part I and postural stability in Part III.

Discussion

The overall factor structure of the Japanese version was consistent with the English version based on the CFIs for all four parts of the MDS-UPDRS in the CFA (all CFI ≥0.93). The Japanese scale was confirmed to share a common factor structure with the English scale. Therefore, this version can be designated as the official Japanese version of the MDS-UPDRS.

EFA, in which variability from sample to sample is expected, identified isolated item differences of factor structure between the Japanese and English versions of the MDS-UPDRS. However, the distribution of factors with their associated eigenvalues and percent variances were similar across the two languages.

In our study, female preponderance was noted as the previous study reported from Japan.[14] This may, in part, be because of the longer life expectancy (by approximately 6.5 years) in Japanese women, in comparison to men.

Another interesting difference between the Japanese- and English-language versions data sets for the MDS-UPDRS concerned the pattern of responses to items 1.1 (cognitive impairment) and 1.2 (hallucinations and psychosis). For the

TABLE 3 Comparison of English-language and Japanese exploratory factor structures for parts I to IV of the MDS-UPDRS

	English		Japanese	
Factor	Eigenvalues	Percent Variance	Eigenvalues	Percent Variance
Part I				
1	4.421	34.0	5.045	42.0
2	1.231	9.5	1.244	10.4
3	1.051	8.1	1.081	9.0
4	1.007	7.7	0.866	7.2
5	0.811	6.2	0.721	6.0
6	0.724	5.6	0.642	5.4
7	0.673	5.2	0.594	5.0
8	0.630	4.8	0.508	4.2
9	0.616	4.7	0.472	3.9
10	0.542	4.2	0.375	3.1
11	0.519	4.0	0.288	2.4
12	0.399	3.1	0.160	1.3
13	0.376	2.9		
Part II				
1	6.898	53.1	7.293	56.1
2	1.128	8.7	1.062	8.2
3	1.000	7.7	0.826	6.4
4	0.728	5.6	0.684	5.3
5	0.595	4.6	0.534	4.1
6	0.542	4.2	0.494	3.8
7	0.425	3.3	0.445	3.4
8	0.390	3.0	0.431	3.3
9	0.380	2.9	0.370	2.8
10	0.294	2.3	0.260	2.0
11	0.245	1.9	0.240	1.8
12	0.198	1.5	0.219	1.7
13	0.178	1.4	0.141	1.1
Part III				
1	12.112	36.7	14.451	43.8
2	5.035	15.3	4.190	12.7
3	2.173	6.6	2.429	7.4
4	2.051	6.2	1.961	5.9
5	1.615	4.9	1.668	5.1
6	1.485	4.5	1.238	3.8
7	1.104	3.3	0.922	2.8
8	0.903	2.7	0.793	2.4
9	0.720	2.2	0.685	2.1
10	0.615	1.9	0.596	1.8
11	0.552	1.7	0.558	1.7
12	0.495	1.5	0.514	1.6
13	0.479	1.5	0.472	1.4
14	0.407	1.2	0.360	1.1
15	0.403	1.2	0.348	1.1
16	0.361	1.1	0.330	1.0
17	0.323	1.0	0.246	0.7
18	0.314	1.0	0.233	0.7
19	0.267	0.8	0.203	0.6
20	0.265	0.8	0.194	0.6
21	0.223	0.7	0.183	0.6
22	0.203	0.6	0.147	0.4
23	0.164	0.5	0.138	0.4
24	0.145	0.4	0.115	0.3
25	0.141	0.4	0.099	0.3
26	0.109	0.3	0.058	0.2
27	0.091	0.3	0.027	0.1
28	0.077	0.2	0.013	0.0
29	0.055	0.2	0.004	0.0
Part IV				
1	3.811	63.9	3.656	60.9
2	0.942	15.6	1.210	20.2
3	0.640	10.7	0.725	12.1
4	0.241	4.0	0.168	2.8
5	0.208	3.5	0.130	2.2
6	0.159	2.3	0.111	1.9

Dotted line shows the factors selected in the English cohort.

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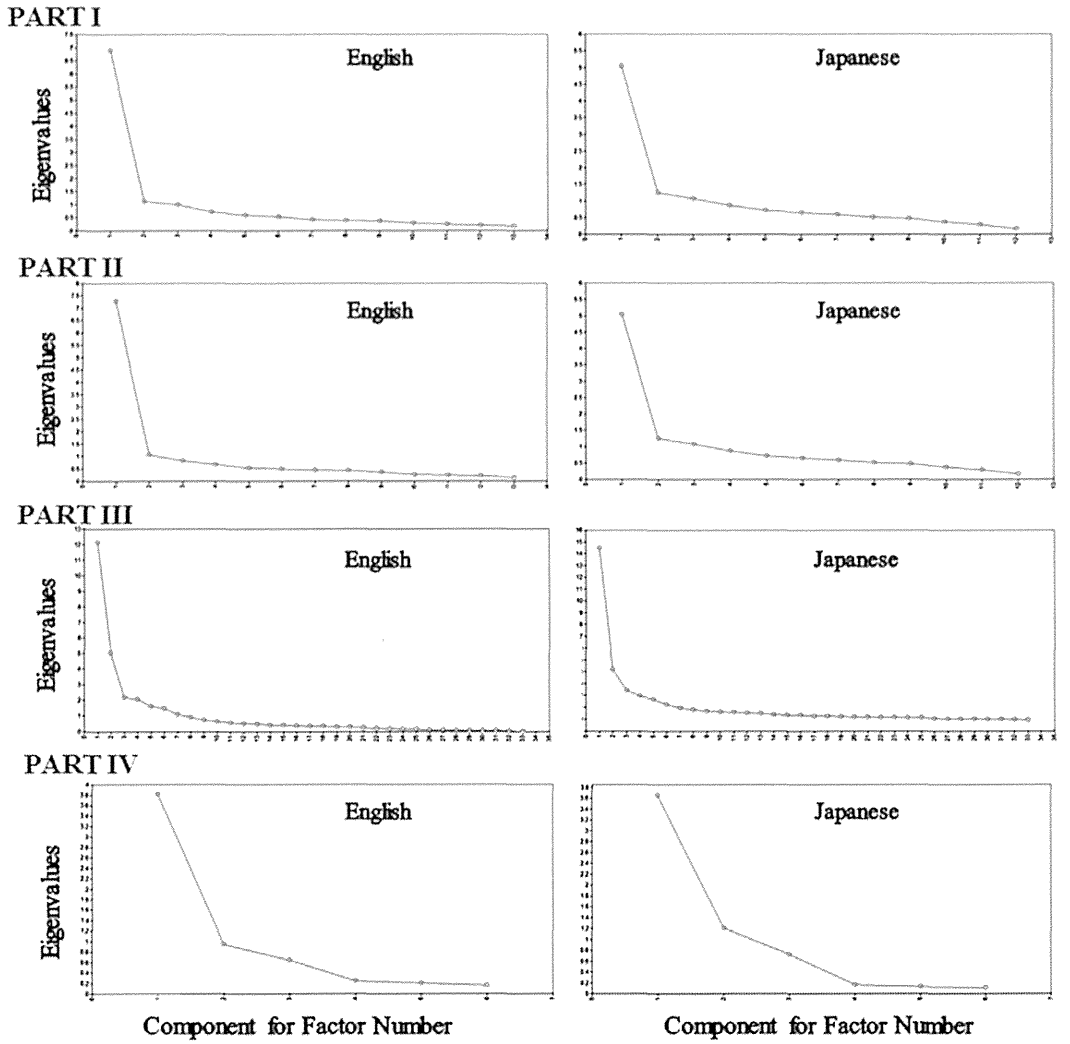

Figure 1 Scree plots for the English and Japanese exploratory factor analyses.

hallucination item, the Japanese and English frequencies for each rating option were very similar (77% and 78%, respectively), but cognitive impairment ratings were different in the two cultures. A much greater percentage (62.2%) of Japanese had 0 scores, in comparison to the English-speaking sample (48.9%). In general, among reports in Western cultures, cognitive impairment and hallucinations are shared or overlapping behaviors and such data have been used to argue shared common pathogeneses.[15,16] Results of the chi-square test indicate that severity of motor and nonmotor symptoms are generally more severe in patients of English groups than those of Japanese groups. Even after taking these differences into consideration, the present results from the Japanese sample may indicate that cognitive impairment is less frequent or viewed differently and thereby may be underreported for cultural reasons in Japan, in comparison to the Western culture.

Contrary to majority of items, constipation problems and postural stability were rated more severe in Japanese patients than English patients. Differences in genetic factor, eating habits, and amount of daily exercise between two populations are possible factors to produce different response to the former item. The reason why postural stability was rated more severely in Japanese groups remains unknown. Factors including examiner's manner to pull patients may be clarified in future.

In conclusion, the CFI for the Japanese version of the MDS-UPDRS was 0.93 or greater. Therefore, the Japanese version meets the criterion for designation as an official translation of the MDS-UPDRS. This is the first Asian- or non-Indo-European–language translation of the MDS-UPDRS. The Japanese version of the MDS-UPDRS is available from the MDS website (http://www.movementdisorders.org/publications/rating_scales/). The establishment of additional non-English translations will further facilitate the understanding of PD symptoms and help accelerate qualified clinical trials and discussions worldwide.

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TABLE 4 Distribution of responses by MDS-UPDRS by language[a]

	English		Japanese			English		Japanese	
Part I									
Cognitive impairment*	Frequency	%	Frequency	%	Daytime sleepiness	Frequency	%	Frequency	%
0	428	48.86	227	62.19	0	212	24.2	104	28.49
1	256	29.22	93	25.48	1	216	24.66	73	20.00
2	121	13.81	25	6.85	2	364	41.55	147	40.27
3	53	6.05	17	4.66	3	59	6.74	32	8.77
4	17	1.94	3	0.82	4	16	1.83	8	2.19
999	1	0.11	0	0.00	999	9	1.03	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Hallucinations and psychosis	Frequency	%	Frequency	%	Pain and other sensations*	Frequency	%	Frequency	%
0	687	78.42	280	76.71	0	303	34.59	148	40.55
1	89	10.16	38	10.41	1	289	32.99	117	32.05
2	51	5.82	26	7.12	2	130	14.84	60	16.44
3	35	4	14	3.84	3	106	12.1	31	8.49
4	13	1.48	4	1.10	4	39	4.45	4	1.10
999	1	0.11	3	0.82	999	9	1.03	5	1.37
Total	876	100	365	100.00	Total	876	100	365	100.00
Depressed mood*	Frequency	%	Frequency	%	Urinary problems	Frequency	%	Frequency	%
0	471	53.77	223	61.10	0	325	37.1	144	39.45
1	265	30.25	84	23.01	1	281	32.08	118	32.33
2	81	9.25	36	9.86	2	137	15.64	60	16.44
3	45	5.14	21	5.75	3	88	10.05	32	8.77
4	12	1.37	0	0.00	4	38	4.34	10	2.74
999	2	0.23	1	0.27	999	7	0.8	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Anxious mood	Frequency	%	Frequency	%	Constipation problems*	Frequency	%	Frequency	%
0	413	47.15	192	52.60	0	384	43.84	90	24.66
1	307	35.05	116	31.78	1	287	32.76	120	32.88
2	96	10.96	39	10.68	2	119	13.58	74	20.27
3	41	4.68	15	4.11	3	70	7.99	63	17.26
4	17	1.94	1	0.27	4	9	1.03	18	4.93
999	2	0.23	2	0.55	999	7	0.8	0	0.00
Total	876	100	365	100.00	Total	876	100	365	100.00
Apathy	Frequency	%	Frequency	%	Lightheadedness on standing*	Frequency	%	Frequency	%
0	584	66.67	249	68.22	0	490	55.94	238	65.21
1	141	16.1	61	16.71	1	216	24.66	78	21.37
2	88	10.05	27	7.40	2	103	11.76	37	10.14
3	52	5.94	20	5.48	3	51	5.82	10	2.74
4	8	0.91	7	1.92	4	9	1.03	1	0.27
999	3	0.34	1	0.27	999	7	0.8	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Features of DDS	Frequency	%	Frequency	%	Fatigue*	Frequency	%	Frequency	%
0	747	85.27	315	86.30	0	217	24.77	141	38.63
1	57	6.51	23	6.30	1	335	38.24	128	35.07
2	44	5.02	20	5.48	2	184	21	57	15.62
3	19	2.17	4	1.10	3	81	9.25	33	9.04
4	6	0.68	0	0.00	4	50	5.71	4	1.10
999	3	0.34	3	0.82	999	9	1.03	2	0.55
Total	876	100	365	100.00	Total	876	100	365	100.00
Sleep problems*	Frequency	%	Frequency	%					
0	280	31.96	138	37.81					
1	202	23.06	103	28.22					
2	207	23.63	81	22.19					
3	140	15.98	39	10.68					
4	40	4.57	3	0.82					
999	7	0.8	1	0.27					
Total	876	100	365	100.00					
Part II									
Speech*	Frequency	%	Frequency	%	Doing hobbies and other activities*	Frequency	%	Frequency	%
0	252	28.77	159	43.56	0	227	25.91	130	35.62
1	236	26.94	78	21.37	1	289	32.99	99	27.12
2	233	26.6	82	22.47	2	185	21.12	65	17.81
3	126	14.38	43	11.78	3	81	9.25	41	11.23

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TABLE 4 (Continued)

	English		Japanese			English		Japanese	
4	22	2.51	3	0.82	4	84	9.59	29	7.95
999	7	0.8	0	0.00	999	10	1.14	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Saliva and drooling*	Frequency	%	Frequency	%	Turning in bed	Frequency	%	Frequency	%
0	341	38.93	186	50.96	0	277	31.62	122	33.42
1	115	13.13	49	13.42	1	378	43.15	144	39.45
2	203	23.17	64	17.53	2	111	12.67	48	13.15
3	157	17.92	46	12.60	3	55	6.28	31	8.49
4	53	6.05	18	4.93	4	50	5.71	19	5.21
999	7	0.8	2	0.55	999	5	0.57	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Chewing and swallowing	Frequency	%	Frequency	%	Tremor*	Frequency	%	Frequency	%
0	549	62.67	241	66.03	0	189	21.58	118	32.33
1	230	26.26	81	22.19	1	360	41.1	154	42.19
2	54	6.16	22	6.03	2	212	24.2	69	18.90
3	34	3.88	18	4.93	3	72	8.22	17	4.66
4	3	0.34	3	0.82	4	36	4.11	7	1.92
999	6	0.68	0	0.00	999	7	0.8	0	0.00
Total	876	100	365	100.00	Total	876	100	365	100.00
Eating tasks	Frequency	%	Frequency	%	Getting out of bed*	Frequency	%	Frequency	%
0	363	41.44	158	43.29	0	180	**20.55**	**101**	27.67
1	265	30.25	114	31.23	1	317	36.19	140	38.36
2	187	21.35	79	21.64	2	199	22.72	73	20.00
3	42	4.79	8	2.19	3	104	11.87	35	9.59
4	10	1.14	5	1.37	4	70	7.99	15	4.11
999	9	1.03	1	0.27	999	6	0.68	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Dressing	Frequency	%	Frequency	%	Walking and balance	Frequency	%	Frequency	%
0	220	25.11	82	22.47	0	184	21	74	20.27
1	322	36.76	176	48.22	1	336	38.36	156	42.74
2	211	24.09	67	18.36	2	105	11.99	38	10.41
3	76	8.68	28	7.67	3	172	19.63	61	16.71
4	42	4.79	12	3.29	4	74	8.45	33	9.04
999	5	0.57	0	0.00	999	5	0.57	3	0.82
Total	876	100	365	100.00	Total	876	100	365	100.00
Hygiene	Frequency	%	Frequency	%	Freezing	Frequency	%	Frequency	%
0	342	39.04	126	34.52	0	453	51.71	176	48.22
1	367	41.89	160	43.84	1	182	20.78	74	20.27
2	88	10.05	47	12.88	2	89	10.16	40	10.96
3	33	3.77	25	6.85	3	90	10.27	49	13.42
4	38	4.34	7	1.92	4	56	6.39	25	6.85
999	8	0.91	0	0.00	999	6	0.68	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Handwriting	Frequency	%	Frequency	%					
0	161	18.38	106	29.04					
1	251	28.65	151	41.37					
2	222	25.34	75	20.55					
3	146	16.67	22	6.03					
Part III									
Speech*	Frequency	%	Frequency	%	Arising from chair	Frequency	%	Frequency	%
0	189	21.58	148	40.55	0	422	48.17	197	53.97
1	379	43.26	143	39.18	1	245	27.97	106	29.04
2	213	24.32	53	14.52	2	78	8.9	24	6.58
3	69	7.88	15	4.11	3	71	8.11	22	6.03
4	22	2.51	4	1.10	4	55	6.28	16	4.38
999	4	0.46	2	0.55	999	5	0.57	0	0.00
Total	876	100	365	100.00	Total	876	100	365	100.00
Facial expression*	Frequency	%	Frequency	%	Gait	Frequency	%	Frequency	%
0	96	10.96	88	24.11	0	202	23.06	81	22.19
1	300	34.25	137	37.53	1	351	40.07	187	51.23
2	361	41.21	109	29.86	2	167	19.06	47	12.88
3	89	10.16	23	6.30	3	97	11.07	36	9.86
4	26	2.97	7	1.92	4	55	6.28	14	3.84
999	4	0.46	1	0.27	999	4	0.46	0	0.00
Total	876	100	365	100.00	Total	876	100	365	100.00
Rigidity, neck	Frequency	%	Frequency	%	Freezing of gait	Frequency	%	Frequency	%
0	260	29.68	134	36.71	0	655	74.77	250	68.49
1	247	28.2	97	26.58	1	95	10.84	50	13.70
2	274	31.28	92	25.21	2	60	6.85	30	8.22
3	73	8.33	36	9.86	3	26	2.97	13	3.56

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TABLE 4 (Continued)

	English		Japanese			English		Japanese	
4	16	1.83	4	1.10	4	38	4.34	19	5.21
999	6	0.68	2	0.55	999	2	0.23	3	0.82
Total	876	100	365	100.00	Total	876	100	365	100.00
Rigidity, RUE*	Frequency	%	Frequency	%	Postural stability*	Frequency	%	Frequency	%
0	176	20.09	93	25.48	0	422	48.17	150	41.10
1	282	32.19	142	38.90	1	157	17.92	66	18.08
2	342	39.04	111	30.41	2	60	6.85	44	12.05
3	69	7.88	14	3.84	3	149	17.01	84	23.01
4	6	0.68	2	0.55	4	86	9.82	20	5.48
999	1	0.11	3	0.82	999	2	0.23	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Rigidity, LUE*	Frequency	%	Frequency	%	Posture	Frequency	%	Frequency	%
0	205	23.4	99	27.12	0	173	19.75	78	21.37
1	268	30.59	135	36.99	1	337	38.47	129	35.34
2	317	36.19	121	33.15	2	206	23.52	84	23.01
3	77	8.79	9	2.47	3	125	14.27	52	14.25
4	7	0.8	1	0.27	4	33	3.77	21	5.75
999	2	0.23	0	0.00	999	2	0.23	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Rigidity, RLE	Frequency	%	Frequency	%	Global spontaneity of movement	Frequency	%	Frequency	%
0	272	31.05	109	29.86	0	108	12.33	49	13.42
1	248	28.31	125	34.25	1	278	31.74	155	42.47
2	275	31.39	106	29.04	2	279	31.85	97	26.58
3	67	7.65	23	6.30	3	184	21	51	13.97
4	10	1.14	1	0.27	4	27	3.08	12	3.29
999	4	0.46	1	0.27	999	0	0	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Rigidity, LLE	Frequency	%	Frequency	%	Postural tremor, right hand	Frequency	%	Frequency	%
0	286	32.65	116	31.78	0	544	62.1	223	61.10
1	227	25.91	120	32.88	1	262	29.91	119	32.60
2	275	31.39	100	27.40	2	43	4.91	19	5.21
3	75	8.56	26	7.12	3	23	2.63	2	0.55
4	11	1.26	1	0.27	4	1	0.11	2	0.55
999	2	0.23	2	0.55	999	3	0.34	0	0.00
Total	876	100	365	100.00	Total	876	100	365	100.00
Finger tapping, right hand*	Frequency	%	Frequency	%	Postural tremor, left hand*	Frequency	%	Frequency	%
0	122	13.93	95	26.03	0	518	59.13	234	64.11
1	342	39.04	167	45.75	1	276	31.51	98	26.85
2	252	28.77	64	17.53	2	49	5.59	27	7.40
3	144	16.44	35	9.59	3	29	3.31	2	0.55
4	15	1.71	3	0.82	4	1	0.11	1	0.27
999	1	0.11	1	0.27	999	3	0.34	3	0.82
Total	876	100	365	100.00	Total	876	100	365	100.00
Finger tapping, left hand*	Frequency	%	Frequency	%	Kinetic tremor, right hand*	Frequency	%	Frequency	%
0	108	12.33	91	24.93	0	546	62.33	258	70.68
1	298	34.02	135	36.99	1	265	30.25	89	24.38
2	265	30.25	96	26.30	2	46	5.25	15	4.11
3	181	20.66	37	10.14	3	13	1.48	1	0.27
4	22	2.51	5	1.37	4	2	0.23	1	0.27
999	2	0.23	1	0.27	999	4	0.46	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Hand movements, right hand*	Frequency	%	Frequency	%	Kinetic tremor, left hand*	Frequency	%	Frequency	%
0	187	21.35	129	35.34	0	493	56.28	236	64.66
1	346	39.5	160	43.84	1	293	33.45	105	28.77
2	231	26.37	57	15.62	2	72	8.22	22	6.03
3	98	11.19	17	4.66	3	14	1.6	1	0.27
4	12	1.37	2	0.55	4	0	0	1	0.27
999	2	0.23	0	0.00	999	4	0.46	0	0.00
Total	876	100	365	100.00	Total	876	100	365	100.00
Hand movements, left hand*	Frequency	%	Frequency	%	Rest tremor amplitude, RUE*	Frequency	%	Frequency	%
0	164	18.72	118	32.33	0	586	66.89	281	76.99
1	311	35.5	147	40.27	1	112	12.79	51	13.97
2	250	28.54	78	21.37	2	121	13.81	26	7.12
3	125	14.27	17	4.66	3	53	6.05	6	1.64

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TABLE 4 (Continued)

	English		Japanese			English		Japanese	
4	25	2.85	4	1.10	4	3	0.34	1	0.27
999	1	0.11	1	0.27	999	1	0.11	0	0.00
Total	876	100	365	100.00	Total	876	100	365	100.00
Pronation: supination movements, right hand*	Frequency	%	Frequency	%	Rest tremor amplitude, LUE*	Frequency	%	Frequency	%
0	199	22.72	100	27.40	0	603	68.84	280	76.71
1	335	38.24	159	43.56	1	120	13.7	56	15.34
2	216	24.66	64	17.53	2	99	11.3	20	5.48
3	107	12.21	35	9.59	3	45	5.14	9	2.47
4	17	1.94	6	1.64	4	5	0.57	0	0.00
999	2	0.23	1	0.27	999	4	0.46	0	0.00
Total	876	100	365	100.00	Total	876	100	365	100.00
Pronation: supination movements, left hand	Frequency	%	Frequency	%	Rest tremor amplitude, RLE	Frequency	%	Frequency	%
0	162	18.49	76	20.82	0	777	88.7	319	87.40
1	297	33.9	138	37.81	1	52	5.94	25	6.85
2	235	26.83	101	27.67	2	35	4	18	4.93
3	150	17.12	42	11.51	3	9	1.03	2	0.55
4	29	3.31	8	2.19	4	0	0	0	0.00
999	3	0.34	0	0.00	999	3	0.34	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Toe tapping, right foot*	Frequency	%	Frequency	%	Rest tremor amplitude, LLE	Frequency	%	Frequency	%
0	168	19.18	89	24.38	0	795	90.75	319	87.40
1	323	36.87	149	40.82	1	46	5.25	24	6.58
2	228	26.03	96	26.30	2	20	2.28	17	4.66
3	129	14.73	24	6.58	3	12	1.37	2	0.55
4	27	3.08	6	1.64	4	0	0	0	0.00
999	1	0.11	1	0.27	999	3	0.34	3	0.82
Total	876	100	365	100.00	Total	876	100	365	100.00
Toe tapping, left foot*	Frequency	%	Frequency	%	Rest tremor amplitude, lip/jaw*	Frequency	%	Frequency	%
0	154	17.58	68	18.63	0	780	89.04	349	95.62
1	251	28.65	140	38.36	1	63	7.19	12	3.29
2	268	30.59	111	30.41	2	18	2.05	3	0.82
3	154	17.58	36	9.86	3	13	1.48	0	0.00
4	46	5.25	10	2.74	4	1	0.11	1	0.27
999	3	0.34	0	0.00	999	1	0.11	0	0.00
Total	876	100	365	100.00	Total	876	100	365	100.00
Leg agility, right leg*	Frequency	%	Frequency	%	Constancy of rest*	Frequency	%	Frequency	%
0	250	28.54	119	32.60	0	409	46.69	219	60.00
1	329	37.56	163	44.66	1	214	24.43	79	21.64
2	190	21.69	61	16.71	2	91	10.39	28	7.67
3	86	9.82	18	4.93	3	85	9.7	21	5.75
4	18	2.05	4	1.10	4	67	7.65	17	4.66
999	3	0.34	0	0.00	999	10	1.14	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Leg agility, left leg*	Frequency	%	Frequency	%					
0	216	24.66	99	27.12					
1	298	34.02	142	38.90					
2	213	24.32	90	24.66					
3	106	12.1	30	8.22					
4	38	4.34	3	0.82					
999	5	0.57	1	0.27					
Total	876	100	365	100.00					
Part IV									
Time spent with dyskinesias*	Frequency	%	Frequency	%	Functional impact of fluctuations	Frequency	%	Frequency	%
0	563	64.27	273	74.79	0	433	49.43	194	53.15
1	173	19.75	41	11.23	1	165	18.84	56	15.34
2	87	9.93	30	8.22	2	81	9.25	32	8.77
3	27	3.08	12	3.29	3	119	13.58	60	16.44
4	17	1.94	6	1.64	4	63	7.19	19	5.21
999	9	1.03	3	0.82	999	15	1.71	4	1.10
Total	876	100	365	100.00	Total	876	100	365	100.00

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TABLE 4 (Continued)

	English		Japanese			English		Japanese	
Functional impact of dyskinesias*	Frequency	%	Frequency	%	Complexity of motor fluctuations*	Frequency	%	Frequency	%
0	695	79.34	308	84.38	0	404	46.12	192	52.60
1	90	10.27	27	7.40	1	291	33.22	125	34.25
2	29	3.31	19	5.21	2	69	7.88	21	5.75
3	46	5.25	7	1.92	3	50	5.71	17	4.66
4	5	0.57	2	0.55	4	46	5.25	3	0.82
999	11	1.26	2	0.55	999	16	1.83	7	1.92
Total	876	100	365	100.00	Total	876	100	365	100.00
Time spent in the OFF state*	Frequency	%	Frequency	%	Painful OFF state dystonia*	Frequency	%	Frequency	%
0	383	43.72	183	50.14	0	680	77.63	319	87.40
1	341	38.93	113	30.96	1	114	13.01	28	7.67
2	106	12.1	50	13.70	2	45	5.14	4	1.10
3	22	2.51	14	3.84	3	13	1.48	6	1.64
4	14	1.6	2	0.55	4	15	1.71	5	1.37
999	10	1.14	3	0.82	999	9	1.03	3	0.82
Total	876	100	365	100.00	Total	876	100	365	100.00

[a]999 = missing.
*$P < 0.05$ by chi-square test (df = 4).
DDS, dopamine dysregulation syndrome; RUE, right upper extremity; LUE, left upper extremity; RLE, right lower extremity; LLE, left lower extremity.

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(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

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Case Report/Case Series

Clinical Correlations With Lewy Body Pathology in *LRRK2*-Related Parkinson Disease

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IMPORTANCE Mutations in leucine-rich repeat kinase 2 (*LRRK2*) are the most common cause of genetic Parkinson disease (PD) known to date. The clinical features of manifesting *LRRK2* mutation carriers are generally indistinguishable from those of patients with sporadic PD. However, some PD cases associated with *LRRK2* mutations lack Lewy bodies (LBs), a neuropathological hallmark of PD. We investigated whether the presence or absence of LBs correlates with different clinical features in *LRRK2*-related PD.

OBSERVATIONS We describe genetic, clinical, and neuropathological findings of 37 cases of *LRRK2*-related PD including 33 published and 4 unpublished cases through October 2013. Among the different mutations, the *LRRK2* p.G2019S mutation was most frequently associated with LB pathology. Nonmotor features of cognitive impairment/dementia, anxiety, and orthostatic hypotension were correlated with the presence of LBs. In contrast, a primarily motor phenotype was associated with a lack of LBs.

CONCLUSIONS AND RELEVANCE To our knowledge, this is the first report of clinicopathological correlations in a series of *LRRK2*-related PD cases. Findings from this selected group of patients with PD demonstrated that parkinsonian motor features can occur in the absence of LBs. However, LB pathology in *LRRK2*-related PD may be a marker for a broader parkinsonian symptom complex including cognitive impairment.

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Mutations in leucine-rich repeat kinase 2 (*LRRK2*) are the most frequent cause of genetic Parkinson disease (PD), accounting for at least 4% of autosomal dominant forms of familial PD and 1% of sporadic PD worldwide.[1] The *LRRK2* gene encodes a large multidomain protein that includes an enzymatically active central region surrounded by a series of putative protein-protein interaction domains.[2] Disease-causing mutations are concentrated within the central region of the protein, which contains an ROC GTPase domain, a COR sequence, and a serine/threonine kinase domain. Thus far, at least 8 mutations (p.N1437H, p.R1441C/G/H, p.Y1699C, p.G2019S, p.I2020T, and possibly p.I1371V) are considered to be pathogenic. p.G2019S is the most frequent mutation but penetrance of p.G2019S and other pathogenic *LRRK2* mutations is incomplete.[3-5]

The clinical presentation of manifesting *LRRK2* mutation carriers tends to be indistinguishable from that of sporadic PD, with mean age at onset of approximately 60 years and appreciable response to levodopa.[6] Conversely, the neuropathological features can be atypical for PD and heterogeneous even within kindreds.[7] In particular, autopsy studies have revealed that Lewy bodies (LBs), which are large intraneuronal protein aggregates consisting primarily of α-synuclein,[8] are absent in a significant subset of cases. This was a surprising finding because LBs are neuropathological hallmarks of PD thought to be central to the neurodegenerative process and the clinical expression of PD and other synucleinopathies. Here we investigated the correlation of clinical features with LB pathology in *LRRK2*-related PD. This may provide insight into the relationship between α-synuclein pathology and specific features of the PD symptom complex.[9]

Methods

All published *LRRK2*-related autopsy cases up to October 2013 were identified by searching for English language articles in PubMed. The search terms *LRRK2*, *Lewy body/bodies*, *pathol-*

Table 1. Demographic and Genetic Features of all *LRRK2* Cases With and Without LB Pathology

Feature	With LBs (n = 17)	Without LBs (n = 20)	*P* Value
Male, % (no./No.)	23.5 (4/17)	40.0 (8/20)	.32
Race/ethnicity			
Non-Asian, % (no./No.)	92.9 (13/14)	57.9 (11/19)	.05
White non-Jewish, No.	10	10	
Ashkenazi Jewish, No.	3	1	
Asian, % (no./No.)	7.1 (1/14)	42.1 (8/19)	
Age at onset, mean (SD), y	56.0 (11.2)	61.0 (10.2)[a]	.17
Disease duration, mean (SD), y	19.2 (9.0)	16.2 (6.7)	.27
Age at death, mean (SD), y	75.2 (9.3)	77.2 (8.4)	.49
LRRK2 mutation			
p.G2019S, % (no./No.)	64.7 (11/17)	30.0 (6/20)	.05
Other, % (no./No.)	35.3 (6/17)	70.0 (14/20)	
p.I2020T, No.	1	8	
p.R1441C, No.	2	2	
p.R1441G, No.	0	2	
p.Y1699C, No.	1	2	
p.N1437H, No.	1	0	
p.I1371V, No.	1	0	

Abbreviations: LB, Lewy body; *LRRK2*, leucine-rich repeat kinase 2.

[a] Seventeen of 20 cases.

Table 2. Demographic Features of *LRRK2* p.G2019S Cases With and Without LB Pathology

Feature	With LBs (n = 11)	Without LBs (n = 6)	*P* Value
Male, % (no./No.)	36.4 (4/11)	50.0 (3/6)	.64
Race/ethnicity			
Ashkenazi Jewish, % (no./No.)	37.5 (3/8)	20.0 (1/5)	>.99
White non-Jewish, % (no./No.)	62.5 (5/8)	80.0 (4/5)	
Asian, % (no./No.)	0 (0/8)	0 (0/5)	
Age at onset, mean (SD), y	57.0 (12.8)	68.0 (7.5)	.07
Disease duration, mean (SD), y	21.1 (9.7)	13.5 (4.2)	.09
Age at death, mean (SD), y	78.1 (6.6)	81.5 (4.1)	.27
Family history of PD, % (no./No.)[a]	50.0 (5/10)	60.0 (3/5)	>.99

Abbreviations: LB, Lewy body; *LRRK2*, leucine-rich repeat kinase 2.

[a] At least 1 first-, second-, and/or third-degree relative with PD.

ogy/pathological, *neuropathology/neuropathological*, and/or *autopsy/autopsies* were used. Additional articles were found by searching the reference lists of identified articles and the authors' own files. Authors of published cases and directors of brain banks were contacted to identify unpublished cases. Clinical data were extracted from published articles. Additional data were obtained by requesting that investigators complete a clinical data form (eFigure in the Supplement) if the patient's clinic record was available. Neuropathological data were extracted from published articles and/or pathology reports when available. Cases were excluded if the associated *LRRK2* mutation was not one of the putative pathogenic mutations (previously mentioned), the patient did not have a clinical diagnosis of PD, or there was minimal or no available clinical and/or pathological information. Epi Info 7 from the Centers for Disease Control and Prevention was used for data analysis (www.cdc.gov/epiinfo/). Categorical variables were compared using the Fisher exact test. Continuous variables were compared using the *t* test. Logistic regression was performed to adjust for disease duration and age at death. Adjustment for Alzheimer disease-related pathology was made, where indicated, using Braak neurofibrillary tangle stage, which was estimated from the available data and dichotomized (≤stage III and ≥ stage IV). When necessary, a flattening constant of 1 was added to each cell to allow an odds ratio to be calculated. No imputation was made for missing data; patients missing values on an outcome were not included in the analysis for that outcome. Because this was an exploratory study, no adjustments were made for multiple comparisons. Separate analyses were also performed for p.G2019S-only cases. The study was approved by the ethics board of the University Health Network, Toronto, Ontario, Canada.

Results

Fifty-nine autopsy cases with *LRRK2* variants were identified: 54 published and 5 unpublished cases. Twenty-two cases were excluded from the analysis: 3 with nonpathogenic variants; 2 nonmanifesting *LRRK2* mutation carriers without a clinical diagnosis of PD; and 17 with insufficient clinical and/or pathological data (eTable 1 in the Supplement). No cases were excluded for neurological disease other than PD. Thirty-seven *LRRK2*-related PD cases were included: 33 published and 4 unpublished cases (17 with LBs and 20 without LBs) (eTable 2 in the Supplement). Neuronal loss within the substantia nigra was reported for all of these cases except for 2, in which these data were not provided. There were very limited data on neuronal loss within other brain regions. The demographic and genetic features of all included cases are summarized in **Table 1**. All cases with a p.I2020T mutation were of Japanese ethnicity. Cases with or without LBs were similar with respect to sex, disease duration, and age at death. Cases with LBs were more likely to have a p.G2019S mutation. The demographic features of p.G2019S cases (11 with LBs and 6 without LBs) are summarized in **Table 2**.

Table 3 provides a summary of the frequency of clinical features in *LRRK2* cases with or without LBs. Tremor was the most common presenting symptom for *LRRK2* patients regardless of the presence of LBs (65% for both groups). Cardinal motor symptoms, atypical features, levodopa responsiveness, and motor complications (see eFigure in the Supplement for details) occurred with similar frequency in both groups for all *LRRK2* cases and for the subset of p.G2019S cases. Certain nonmotor features (documented on history and/or examination) were more frequent among *LRRK2* cases with LBs. After adjusting for disease duration and age at death, cognitive impairment/dementia, anxiety, and orthostatic hypotension were associated with the presence of LBs (**Table 4**). Cognitive impairment/dementia and

Table 3. Frequency of Clinical Features With or Without LB Pathology[a]

Feature	All *LRRK2* Cases (N = 37)			*LRRK2* p.G2019S Cases (n = 17)		
	With LBs (n = 17)	Without LBs (n = 20)	*P* Value	With LBs (n = 11)	Without LBs (n = 6)	*P* Value
Motor features, % (no./No.)						
Bradykinesia	100 (17/17)	100 (18/18)	>.99	100 (11/11)	100 (5/5)	>.99
Rigidity	100 (17/17)	100 (15/15)	>.99	100 (11/11)	100 (6/6)	>.99
Tremor	94 (16/17)	94 (16/17)	>.99	91 (10/11)	100 (6/6)	>.99
Postural instability	100 (16/16)	92 (12/13)	.45	100 (11/11)	80 (4/5)	.31
Atypical features	17 (2/12)[b,c]	33 (3/9)[d]	.61	11 (1/9)[c]	0 (0/3)	>.99
Nonmotor features, % (no./No.)						
Cognitive impairment/dementia	**67 (10/15)**	**20 (4/20)**	**.01**	**82 (9/11)**	**17 (1/6)**	**.03**
Depression	79 (11/14)	38 (3/8)	.08	89 (8/9)	67 (2/3)	.45
Anxiety	**82 (9/11)**	**0 (0/7)**	**.002**	**100 (8/8)**	**0 (0/3)**	**.006**
Orthostatic hypotension	**50 (6/12)**	**0 (0/13)**	**.005**	63 (5/8)	0 (0/3)	.18
Urinary symptoms	40 (4/10)	25 (3/12)	.65	57 (4/7)	0 (0/2)	.44
Constipation	78 (7/9)	38 (5/13)	.10	100 (6/6)	100 (2/2)	>.99
Levodopa treatment, % (no./No.)						
Positive response[e]	80 (8/10)[f]	86 (12/14)[g]	>.99	71 (5/7)	60 (3/5)[g]	>.99
Fluctuations	67 (10/15)	80 (12/15)	.68	64 (7/11)	67 (4/6)	>.99
Dyskinesia	73 (11/15)	62 (8/13)	.69	80 (8/10)	50 (3/6)	.30
Maximum levodopa dose, mean (SD), mg	798 (431)	836 (504)	.85	741 (395)	840 (391)	.67
No. of cases	10	11		8	5	

Abbreviations: LB, Lewy body; *LRRK2*, leucine-rich repeat kinase 2.

[a] The results for the features in bold are statistically significant.

[b] One patient had supranuclear gaze palsy.

[c] One patient had upper motor neuron signs and myoclonus.

[d] One patient had upper motor neuron signs, 1 patient had supranuclear gaze palsy and upper motor neuron signs, and 1 patient had amyotrophy.

[e] Percentage of patients with moderate to marked levodopa response.

[f] One patient did not have a trial of levodopa.

[g] One patient could not tolerate levodopa.

anxiety were also associated with the presence of LBs within the subgroup of cases with the p.G2019S mutation. The association between cognitive impairment/dementia and the presence of LBs was maintained after adjustment for the degree of Alzheimer disease-related pathology (odds ratio, 8.14; 95% CI, 1.46-45.47; $P = .02$ for all *LRRK2* cases and odds ratio, 76.03; 95% CI, 1.07-5414.76; $P = .047$ for only p.G2019S cases).

Discussion

To our knowledge, this study is the first report of clinicopathological correlations in a series of *LRRK2*-related PD cases. We found that a primarily motor phenotype was associated with an absence of LBs. Parkinsonism (ie, bradykinesia plus rigidity, tremor, and/or postural instability) occurring independently of LB pathology has also been observed in the context of mutations in *PARK2*, which encodes parkin, where most autopsy reports describe an absence of LBs.[10] Conversely, LBs have been detected in the brains of people without the motor features of PD, an entity termed *incidental LB disease*. Our findings are consistent with these observations that LBs are neither necessary nor sufficient for the clinical expression of parkinsonism. Yet, there is strong evidence in experimental mouse models of PD that accumulation of α-synuclein aggregates in the substantia nigra pars compacta is associated with the death of dopaminergic neurons that harbor these aggregates with concomitant loss of tyrosine hydroxylase and dopamine metabolites in the dorsal striatum.[11] There is similar evidence linking α-synuclein aggregates in hippocampus to hippocampal neuron loss and cognitive impairment.[12] It is proposed that the neuropathological correlate of parkinsonian motor features is neuronal loss in the ventrolateral tier of the substantia nigra pars compacta.[8] However, loss of nigral neurons is also not specific for a diagnosis of PD because it occurs in many other neurodegenerative disorders with prominent parkinsonism such as progressive supranuclear palsy and multiple system atrophy.

The expression of nonmotor features in this series of *LRRK2*-related PD cases was found to be related to the presence of LBs. In particular, cognitive impairment/dementia, anxiety, and orthostatic hypotension were more likely to occur at some point during the disease course in patients who were found to have LBs at autopsy. Many nonmotor features tend to occur with longer disease duration and/or older age[13] but we did not find that these potential confounders accounted for the differences observed between those with or without LBs. Evidence for an association between Lewy pathology and nonmotor symptoms has been previously demonstrated for cognitive impairment in PD. In particular, several studies have demonstrated a

Table 4. Clinical Correlates of LB Pathology in *LRRK2*-Associated Parkinson Disease[a,b]

	All *LRRK2* Cases (N = 37)		*LRRK2* p.G2019S Cases (n = 17)	
Feature	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Motor features				
Bradykinesia	0.95 (0.05-17.97)	.97	2.49 (0.08-80.81)	.61
Rigidity	1.22 (0.06-26.80)	.90	1.94 (0.07-53.77)	.69
Tremor	1.03 (0.04-26.52)	.99	0.60 (0.04-9.19)	.71
Postural instability	2.22 (0.16-30.44)	.55	4.55 (0.23-89.65)	.32
Atypical features	0.54 (0.05-6.19)	.62	1.38 (0.08-25.39)	.83
Nonmotor features				
Cognitive impairment/dementia	**9.74 (1.80-52.60)**	**.008**	**85.64 (1.52-4817.27)**	**.03**
Depression	3.06 (0.36-26.07)	.31	3.33 (0.06-184.51)	.56
Anxiety	**17.87 (1.37-233.28)**	**.03**	**24.69 (1.14-536.51)**	**.04**
Orthostatic hypotension	**12.03 (1.17-123.93)**	**.04**	4.35 (0.31-61.10)	.28
Urinary symptoms	2.25 (0.29-17.46)	.44	6.82 (0.36-130.83)	.20
Constipation	14.49 (0.78-267.71)	.07	1.95 (0.06-68.51)	.71
Levodopa treatment				
Positive response	0.11 (0.01-2.42)	.16	0.10 (0-3.21)	.19
Fluctuations	0.10 (0.01-1.53)	.10	0.14 (0.01-3.31)	.22
Dyskinesia	0.31 (0.02-4.72)	.40	0.92 (0.05-16.14)	.95

Abbreviations: LB, Lewy body; *LRRK2*, leucine-rich repeat kinase 2; OR, odds ratio.

[a] Adjusted for disease duration and age at death.

[b] The results for the features in bold are statistically significant.

strong correlation between dementia and severity of cortical Lewy pathology.[14-16]

Based on our findings, we hypothesize that *LRRK2*-related PD with LBs is associated with more extensive neurodegeneration whereas neuronal loss may be more restricted (eg, to the substantia nigra pars compacta) in cases lacking LBs. This would be similar to parkin-related PD in which there is frequently an absence of LBs, restricted neurodegeneration, and a relative lack of nonmotor features.[10] In patients with sporadic PD, cortical Lewy pathology correlates with dementia but Alzheimer disease plaques and tangles also contribute to their cognitive impairment.[16,17] It is possible that aggregates of proteins other than α-synuclein are contributors to the clinical expression of *LRRK2*-related PD. Standardized neuropathological assessments of a series of *LRRK2* autopsy cases, including semiquantitative measures of neuronal loss and examination of various protein aggregates in brain stem, subcortical, and cortical structures, are needed to further interrogate correlations with specific motor and nonmotor symptoms in *LRRK2*-related PD.

Prior reports have highlighted the occurrence of atypical neuropathological findings at autopsy for some manifesting *LRRK2* mutation carriers including pathology resembling progressive supranuclear palsy, multiple system atrophy, or frontotemporal lobar degeneration with ubiquitin-positive inclusions, presence of TDP-43 inclusions, and/or lack of LB pathology (eTable 2). Our assessment was limited to clinical correlations with LBs because this was the only neuropathological feature available for all cases. Additional details—such as the presence of α-synuclein immunoreactive inclusions in neuronal processes (eg, Lewy neurites, dotlike structures, and axonal spheroids), degree of neuronal loss, involvement of extranigral structures, immunostaining results for other protein inclusions, and the distribution of these features—were unavailable for many cases so analysis of these other features could not be carried out here. Furthermore, there is a lack of standard operating procedures for the neuropathological diagnosis of PD[8] and methodological differences (eg, areas sampled, immunostaining performed, and types of antibodies used) among the different centers may have produced variable results. Ongoing and future efforts to standardize autopsy collection, handling, and reporting for *LRRK2*-related PD cases will help to provide data for more detailed clinicopathological correlations.

The *LRRK2* autopsy cases used in this study were identified primarily from published reports; therefore, there is the potential for ascertainment bias. Furthermore, the cases came from differing sources (eg, individual cases, large kindreds, and brain banks). The clinical data acquired in the study were based on retrospective reports by the patients, caregivers, and/or treating physician. The nature of this study precluded standardized clinical assessments, which is a significant limitation. An additional limitation includes the potential for false-positive findings due to multiple comparisons. Regardless, our observations raise the hypothesis that LB pathology may be the underlying basis for cognitive dysfunction in *LRRK2* disease while at the same time being a marker for a broader parkinsonian symptom complex in *LRRK2*-related PD. This can be tested in future prospective cohort studies of patients with *LRRK2* mutations.

An important unresolved question is: why are LBs absent in a subset of patients with *LRRK2*-related PD? The large number of cases reported from various centers demonstrates that LB-negative *LRRK2*-related PD is not an anomalous finding. Genotype cannot account for this finding because the subset of patients without LBs is not represented by 1 specific *LRRK2* mutation. The possibility that *LRRK2*-related PD represents a distinct disease from sporadic PD and thus can present with non-LB pathology is unlikely based on the significant clinical similarities between PD associated with *LRRK2* mutations and

sporadic PD,[6] evidence from genome-wide association studies demonstrating that *LRRK2* polymorphisms are genetic risk factors for sporadic PD,[18] and experimental findings that implicate the LRRK2 protein in molecular pathways underlying PD pathogenesis.[2] While our study did not explain why LBs are sometimes absent in *LRRK2*-related PD, it contributes to the accumulating evidence that LBs alone cannot explain the pathogenesis of PD but other forms of α-synuclein may also play important roles.[19] Indeed, small soluble aggregates of α-synuclein have been isolated from the cortex of a patient with G2019S *LRRK2* PD without LBs.[20] Our study also supports the ongoing effort to reevaluate the pathological criteria used to define PD, in particular, deemphasizing LBs as a core feature.[21]

Conclusions

Lewy body pathology is not present in all patients with *LRRK2*-related PD. The mutation p.G2019S is more frequently associated with LB pathology compared with other *LRRK2* mutations. The classic parkinsonian motor symptoms can occur without LBs, and a primarily motor phenotype appears to be associated with an absence of LBs. The expression of certain nonmotor features, particularly cognitive impairment, anxiety, and orthostatic hypotension, is related to the presence of LBs. Thus, LB pathology in *LRRK2*-related PD may be a marker for a broader parkinsonian symptom complex.

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Author Contributions: Drs Kalia and Marras had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kalia, Lang, Hazrati, Marras.
Acquisition, analysis, or interpretation of data: All authors.
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Conflict of Interest Disclosures: Dr Kalia has received educational support from Allergan. Dr Lang has served as an advisor for Abbott, Abbvie, Allon Therapeutics, Avanir Pharmaceuticals, Biogen Idec, Boerhinger-Ingelheim, Ceregene, Medtronic, Merck, Novartis, NeuroPhage Pharmaceuticals, Teva Pharmaceuticals, and UCB; has received publishing royalties from Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press; and has served as an expert witness in cases related to the welding industry. Mayo Clinic and Dr Wszolek have a financial interest in technologies titled, "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 Dr Wszolek has received royalties through Mayo Clinic in accordance with its royalty-sharing policies. Dr Trojanowski has received funding for travel and honoraria from Takeda Pharmaceutical Co Ltd; has received speaker honoraria from Pfizer Inc; and serves as an associate editor of *Alzheimer's & Dementia*. Dr Trojanowski may accrue revenue on patents regarding a 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 α-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. Dr Tolosa has served as a consultant to Novartis, Teva Pharmaceuticals, Boerhinger-Ingelheim, UCB, Lundbeck, and Abbvie. Dr Langston has received funding from Teva Pharmaceuticals. Dr Hasegawa has received honoraria from Boerhinger-Ingelheim, GlaxoSmithKline, Kyowa Hakko Kirin Co, Novartis, Otsuka Pharmaceutical Co, and Dainippon Sumitomo Pharm Co. Dr Brice has received honoraria from Lundbeck. Dr Stoessl has served as an advisor for Abbott, Abbvie, Biogen Idec, Medgenesis, and UCB and has received honoraria from Teva Pharmaceuticals. Dr Marras has received honoraria for teaching from EMD Serono. No other disclosures were reported.

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Research article

Possible involvement of iron-induced oxidative insults in neurodegeneration

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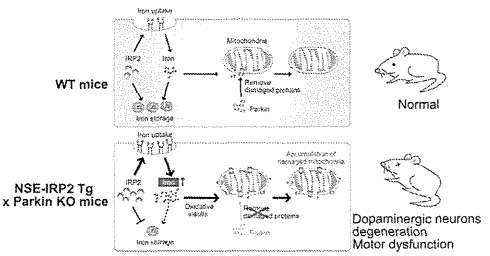
HIGHLIGHTS

- Increase of IRP2 accumulates iron that can provoke mitochondrial oxidative insults.
- Mitochondrial oxidative insults are induced in neurons in IRP2 transgenic (Tg) mice.
- Parkin appears involved in removal of iron-induced mitochondrial oxidative insults.
- IRP2 increase degenerates dopaminergic neurons synergistically with loss of Parkin.
- The IRP2 Tg mice may be useful to probe the roles of iron in neurodegeneration.

GRAPHICAL ABSTRACT



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ABSTRACT

Involvement of iron in the development of neurodegenerative disorders has long been suggested, and iron that cannot be stored properly is suggested to induce iron toxicity. To enhance iron uptake and suppress iron storage in neurons, we generated transgenic (Tg) mice expressing iron regulatory protein 2 (IRP2), a major regulator of iron metabolism, in a neuron-specific manner. Although very subtle, IRP2 was expressed in all regions of brain examined. In the Tg mice, mitochondrial oxidative insults were observed including generation of 4-hydroxynonenal modified proteins, which appeared to be removed by a mitochondrial quality control protein Parkin. Inter-crossing of the Tg mice to Parkin knockout mice

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