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Sex differences in LRRK2 G2019S and idiopathic Parkinson's Disease

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Abstract

Objective: To evaluate sex differences and the relative effect of G2019S *LRRK2* mutations in Parkinson's disease (PD). **Methods**: 530 *LRRK2* PD carriers and 759 noncarrier PD (idiopathic, IPD) evaluated as part of the Fox Foundation (MJFF) Consortium were included. All participants completed a study visit including information on clinical features, treatment, examination, and motor and nonmotor questionnaires. Clinical features were compared between men and women separately for IPD and *LRRK2* PD; and features were compared between IPD and *LRRK2* PD separately for men and women. **Results**: *Among IPD*: men had higher levodopa equivalency dose (LED), worse activities of daily living and motoric severity but lower complications of therapy (UPDRS-IV). IPD women had higher olfaction and thermoregulatory scores and were more likely to report family history of PD. Among *LRRK2 PD*: Male predominance was not observed among G2019S *LRRK2* cases. Women had worse UPDRS-IV but better olfaction. *Among same sex*: *LRRK2* men and women had better olfaction than IPD counterparts. *LRRK2* men demonstrated lower motor and higher cognitive, RBD and thermoregulation scores than IPD men and *LRRK2* women had greater UDPRS-IV and rates of dyskinesia. **Interpretation**: There were clinical differences between sexes with a more severe phenotype in IPD men and more complications of therapy in women. The more severe male phenotype was moderated by *LRRK2*, with *LRRK2* men and women showing less diversity of phenotype. Our study supports that both genetics and sex drive phenotype, and thus trials in *LRRK2* and IPD should consider gender stratification in design or analysis.

Introduction

Clinical and epidemiological features of Parkinson's disease (PD) vary between men and women.[1] This is pronounced in western countries where men are approximately 1.5 times more likely to develop PD than women.[2–8] Sex differences may be attributable to genetics, sexual brain dimorphism, hormonal, and immunological factors, environmental exposures, referral bias, treatment differences, or a combination of these. The study of Leucine Rich Repeat Kinase 2 gene (*LRRK2*) mutation carriers provides a unique window to disentangle these elements. Sex differences have variably been observed in *LRRK2* PD, however, the degree to which these are due to mutation effects or overall differences between men and women has not been well elucidated.

Evaluation of the large number of mutation positive and negative PD subjects in the Michael J Fox Foundation (MJFF) LRRK2 Consortium provides a unique opportunity to study the relative effect of carrying a *LRRK2* mutation and the role of gene status on sex differences. In this analysis, we focus on the most prevalent *LRRK2* mutation, the G2019S, and report comparisons of motor and nonmotor features in a large sample of PD cases with and without this mutation. This allows separation of the role of the gene on women and men with PD, as well as examination of differences in men and women with *LRRK2* mutations.

Subjects/materials and Methods

Subjects

Subjects were enrolled in the MJFF LRRK2 Consortium, and the analysis was restricted to those with G2019S mutations. Description of study cohorts of the MJFF LRRK2 Consortium, and determination of *LRRK2* status are as described (www.michaeljfox.org).[9] Data from the July 2014 data cut were utilized. A total of 1289 cases with PD, including 530 *LRRK2* PD carriers and 759 noncarrier idiopathic or genetically undefined PD (IPD), were included. Most enrolled participants were unaware of their genetic status. While measures varied slightly between sites, all participants completed a study visit that included historical information on clinical features and treatment, neurological examination including quantitative motor measures utilizing the Unified Parkinson Disease Rating Scale (UPDRS,[10]) and MDS-UPDRS[11] Hoehn and Yahr rating scale,[12] and disability from the Schwab-England rating scale. Information on nonmotor PD features included measures of cognition (Montreal Cognitive Assessment, MoCA,[13]), mood (Geriatric Depression scale, abbreviated version GDS15,[14] Beck Depression Inventory, BDI[15]), dysautonomia (SCOPA-AUT,[16]), olfaction (UPSIT[17]), and sleep (Epworth Sleepiness Scale, ESS[18] and REM sleep behavior disorder questionnaire, RBDSQ[19]). However, because of the large number of missing responses, the sexual questions were not analyzed in either group in the SCOPA-AUT. UPDRS Part II and III subscores were converted to MDS UPDRS scores using previously published conversion formulas.[20]

Analysis and sample size considerations

In order to disentangle the degree to which sex differences were related to gene effects, two stratified analyses were performed. First, to determine the sex differences within genetic groups, motor and nonmotor features were compared between men and women with IPD and men and women with *LRRK2* PD. Second, in order to further assess whether there is a sex-specific effect associated with gene mutation, features were compared between men with IPD and *LRRK2* PD and between women with IPD and *LRRK2* PD. Basic descriptive statistics (e.g., means, standard deviations, frequencies) for all markers of interest were computed. Means and standard deviation are presented for normally distributed continuous variables and median and interquartile range for nonnormally distributed data. Prior to analyses, variables were examined for outliers. All statistical data analysis was performed using STATA13 (STATA Corp., College Station, TX). Two-sample t-tests or nonparametric equivalent in unadjusted analyses and linear regression models in adjusted analyses, adjusting for age, disease duration and levodopa equivalent dosing (LED), and other covariates when applicable (i.e., education years), were applied to compare continuous clinical features between men and women with IPD and with *LRRK2*-related PD. Chi-square tests in unadjusted analyses and logistic regression models in adjusted analyses were used to compare categorical variables. In order to adjust the significance level given the large number of comparisons performed in this mostly exploratory analysis, we compromised a significance level of 0.01 as threshold for declaring statistical significance for all analyses.[9]

Results

Demographic information and motor and nonmotor comparisons are reported in Tables 1–6. Male predominance was observed in IPD but not in *LRRK2* PD (60:41 vs. 52:48, approaching significance at $P = 0.01$). Overall as a group, subjects with *LRRK2* PD had a younger onset of PD by approximately 3 years, longer disease duration at study exam, and were on higher LED than those with IPD, as described in detail recently.[9] As expected, having a *LRRK2* mutation was associated with higher proportion of positive family history in first (42.9 vs. 22.2, $P < 0.001$) and second-degree relatives (23.2 vs. 12.7, $P < 0.001$).

Gender effects within the same genetic etiology

Gender differences in IPD

Motor features (Table 2)

Among those with IPD, men and women had similar age at exam, age at PD onset and diagnosis, and similar disease duration (Table 1). However, men were on higher LED than women (median dose 375 vs. 200 mg/d, $P = 0.001$). In a multivariate model adjusting for age, disease onset

Table 1. Gender effects within the same genetic etiology, disease demographics.

	IPD				LRRK-PD				*P*-value all IPD vs all LRRK2-PD
	All	Women	Men	*P*-value	All	Women	Men	*P*-value	
N (%)	759	311 (41)	448 (59)		530	254 (47.9)	276 (52)		0.013
Age in years (mean ± SD)	66.17 ± 11.7	65.7 ± 11.4	66.5 ± 11.8	0.36	65.6 ± 11.6	65.7 ± 11.4	65.5 ± 11.8	0.86	0.38
Age at PD onset (mean ± SD)	58.7 ± 12.5	58 ± 12.4	59.1 ± 12.6	0.24	55.7 ± 11.3	55.8 ± 11.2	55.7 ± 11.4	0.95	<0.001
Age at PD diagnosis (mean ± SD)	62.7 ± 11.1	62.1 ± 11	63 ± 11.1	0.39	57.3 ± 11.4	58.1 ± 11	56.6 ± 11.6	0.24	<0.001
Disease duration in years (mean ± SD)	7.5 ± 6.1	7.7 ± 6.6	7.4 ± 5.8	0.93	9.6 ± 6.7	9.5 ± 6.9	9.7 ± 6.3	0.46	<0.001
LED in mg/d (median, IQR)	300 (600)	200 (450)	375 (615)	0.001	500 (687.5)	417.5 (677)	562.5 (760)	0.11	<0.001
Family History of PD in first degree relative (*n*, %)	116 (22.2)	56 (27.2)	60 (19)	0.03	151 (42.9)	78 (45.6)	73 (40.3)	0.31	<0.001
Family History of PD in second-degree relative (*n*, %)	64 (12.7)	27 (13.6)	37 (12.2)	0.63	70 (22.4)	35 (23.2)	35 (21.6)	0.74	<0.001

and LED, men trended toward slightly higher scores on the UPDRS activities of daily living subscore (converted UPDRS-II or MDS-UPDRS-II) and worse motoric severity as measured by the MDS-UPDRS-III (or converted UPDRS-III), although neither comparison reached the predetermined significance level. The domain that was of greatest difference in UPDRS-III scores was worse rigidity subscores in men. In turn, women had slightly worse UPDRS-IV in the adjusted model but also did not reach statistical significance. Rates of disease asymmetry, presence of severe LID and presence/absence of different cardinal signs including rest tremor at a diagnostic checklist were not different between genders. Women reported a greater frequency of positive family history of PD in a first degree relative (18.9 vs. 27.2), ($P = 0.03$), although not at the 0.01 significance level.

Nonmotor features (Table 3)

While IPD women had worse depression scores than men, this difference was not significant when adjusted by age, disease duration and LED (5.6 vs. 5.0, $P = 0.99$). Women had better olfaction scores as measured by raw total UPSIT scores (17.2 vs. 21.1, $P < 0.001$) although the proportion of hyposmic individuals was similar in the multivariate model (82.2 vs. 78.7, $P = 0.61$). There were no gender differences in IPD in regards to MoCA scores when adjusted by age, disease duration and education years. There were also no differences in the ESS and RBDQ total and categorized scores between men and women. While there were no differences in total SCOPA-AUT scores, the cardiac and thermoregulatory subscores were slightly higher in women (mean scores 1.1 vs. 1.5, $P = 0.01$; 2.2 vs. 3.2, $P = 0.001$, respectively).

Gender differences in *LRRK2*-PD

Motor features (Table 2)

In *LRRK2*-PD, men and women also had similar age at exam, age at PD onset and diagnosis, and disease duration. Both men and women reported similar rates of positive family history for PD in first- and second-degree relatives (40.3 vs. 45.6, $P = 0.31$, and 23.2 vs. 21.6, $P = 0.74$). While men had a tendency to higher LED, this difference was not statistically significant (median dose for women 417 (677) vs. men, 562.5 (760), $P = 0.11$, Table 1). In the multivariate adjusted model, *LRRK2*-PD men and women had similar UPDRS-I, MDS-UPDRS-II and MDS-UPDRS-III. Disease severity appeared, however, to be differentially driven: by rigidity in men (mean 3.7 vs. 4.4, $P = 0.006$), and bradykinesia in women (mean 8.2 vs. 7.3, $P = 0.007$). UPDRS-IV was slightly higher in *LRRK2* women than men (median 2 (6) vs. 2 (4.5), $P = 0.01$). Rates of disease asymmetry, severe LID, and ever presence of different cardinal signs including rest tremor were similar between genders.

Table 2. Gender effects within the same genetic etiology, motor features.

	IPD				LRRK-PD				*P*-value all IPD vs all LRRK2-PD*
	All	Women	Men	*P*-value*	All	Women	Men	*P*-value*	
UPDRS-I, ON medication (median, IQR)	1 (3)	1 (3)	2 (2)	0.34	2 (2.5)	1 (3)	2 (2)	0.67	0.32
MDS-UPDRS-II or converted UPDRS_II, ON medication (median, IQR)	11.7 (10.7)	11 (9.9)	12.3 (11)	0.03	12.1 (13.7)	12.3 (14.2)	12 (11.3)	0.45	0.14
MDS-UPDRS-III, or converted UPDRS_III, ON medication (mean±SD)	32.2 ± 17.4	31.8 ± 18.1	32.5 ± 16.8	0.02	32.2 ± 19.1	33.2 ± 20.6	31.4 ± 17.6	0.82	0.006
UPDRS-III subscores (mean ± SD)									
Balance/gait	6.4 ± 4.5	5.6 ± 4.4	6.9 ± 4.5	0.20	6.9 ± 5.2	6.8 ± 5.7	6.9 ± 5.6	0.54	
Rest tremor	1.5 ± 1.8	1.5 ± 1.7	1.5 ± 1.8	0.59	1.4 ± 1.9	1.3 ± 2	1.4 ± 1.9	0.39	
Rigidity	4.3 ± 3.3	3.4 ± 2.6	4.8 ± 3.6	0.001	4.1 ± 3.5	3.7 ± 3.4	4.4 ± 3.5	0.006	
Bradykinesia	8.1 ± 5.3	7.7 ± 5	8.3 ± 5.5	0.23	7.8 ± 6.1	8.2 ± 6.2	7.3 ± 5.9	0.007	
UPDRS-IV, ON medication (median, IQR)	1 (2)	1 (2)	1 (2)	0.03	2 (4)	2 (6)	2 (4.5)	0.01	0.04
Asymmetric onset (*n*, %)	396 (80.5)	160 (83.8)	236 (78.4)	0.64	283 (91)	138 (91.2)	145 (91.8)	0.78	0.02
Severe L-dopa induced dyskinesias** (*n*, %)	26 (3.6)	12 (4.1)	14 (3.2)	0.81	41 (8.2)	18 (7.5)	23 (8.8)	0.36	0.001
Ever present:**									
Bradykinesia	720 (96.6)	296 (96.4)	424 (96.8)	0.22	459 (95.2)	223 (95.7)	236 (94.8)	0.17	0.15
Rigidity	681 (91.5)	281 (91.5)	400 (91.5)	0.10	427 (88.4)	207 (88.8)	220 (88)	0.44	0.11
Rest Tremor	604 (83.2)	255 (86.4)	349 (81)	0.24	386 (82.8)	183 (81)	203 (84.6)	0.09	0.73

*Adjusted *P*-values (for age, disease duration, and LED),
**Derived from diagnostic check list.

Nonmotor features (Table 3)

GDS15 scores did not differ in the adjusted model. Within *LRRK2*, similar to IPD, women had better olfaction measured by total raw UPSIT scores (24.4 vs. 20.9, $P < 0.001$), but similar rates of hyposmia (55.8 vs. 64.7, $P = 0.3$). They also had similar MoCA and sleep rating scales scores. Similar to IPD, there were no differences in total SCOPA-AUT scores, although thermoregulatory scores trended toward being higher in women (3.4 vs. 2.7, $P = 0.03$).

LRRK2 G2019S effects within the same gender

Demographic, motor, and nonmotor features are reported in Tables 4–6. Among women with PD, almost 45% harbored a G2019S *LRRK2* mutation, compared to approximately 38% of men (44.9 vs. 38.1, $P = 0.01$).

Gene effects among women

Motor features (Table 5)

PD severity and disability was similar between IPD and *LRRK2*-PD women, with comparable total UPDRS Part I, MDS-UPDRS-II, and MDS-UPDRS-III. UPDRS-IV subscores and rate of severe levodopa dyskinesias were, however, greater in women, although neither reached the stringent level of significance of 0.01. IPD women had higher rates of rigidity (defined as ever present from a diagnostic check list, 88.8 vs. 91.5, $P = 0.001$), although rigidity subscores at exam measured by UPDRS-III were not different (3.7 vs. 3.4, $P = 0.85$).

Table 3. Gender effects within the same genetic etiology, nonmotor features.

	IPD				LRRK-PD				*P*-value all IPD vs. all LRRK2-PD*
	All	Women	Men	*P*-value*	All	Women	Men	*P*-value*	
GDS15 (mean ± SD)	5 ± 4.1	5.6 ± 4.3	5 ± 3.9	0.99	5.4 ± 4.2	5.7 ± 4.3	5 ± 4	0.42	0.51
Total UPSIT score (mean ± SD)	18.7 ± 7.2	21.1 ± 7.1	17.2 ± 6.9	<0.001	22.6 ± 8.3	24.4 ± 8.2	20.9 ± 8	0.001	<0.001
Hyposmic (*n*, %)	131 (80.9)	48 (78.7)	83 (82.2)	0.61	160 (60.4)	72 (55.8)	88 (64.7)	0.30	<0.001
Total MoCA score (mean ± SD)	24.5 ± 4.4	25 ± 4.3	24.1 ± 4.4	0.30	24.1 ± 4.3	24.2 ± 4.5	24.1 ± 4.2	0.73	0.08
Epworth Sleepiness Scale total score (mean ± SD)	5.5 ± 5.1	5 ± 4.9	5.9 ± 5.1	0.87	6.6 ± 5.4	6.5 ± 5.4	6.7 ± 5.4	0.55	0.16
RBDQ Total (mean ± SD)	5.2 ± 3.1	5.2 ± 3.4	5.1 ± 3	0.76	3.5 ± 2.6	3.3 ± 2.6	3.6 ± 2.9	0.63	0.001
SCOPA-AUT Total score	14.3 ± 9.5	15.2 ± 10.1	13.6 ± 8.9	0.06	14.5 ± 10.1	15.1 ± 10.8	14 ± 9.5	0.27	0.28
Gastrointestinal	4.5 ± 3.4	4.5 ± 3.4	4.4 ± 3.5	0.27	4.1 ± 3.6	4.2 ± 3.9	4 ± 3.3	0.49	
Urinary	5.3 ± 4.4	5 ± 4.5	5.5 ± 4.4	0.09	5.8 ± 5.2	5.6 ± 5.2	5.9 ± 5.2	0.66	
Cardio	1.2 ± 1.5	1.5 ± 1.5	1.1 ± 1.4	0.01	1.1 ± 1.6	1.2 ± 1.7	1 ± 1.5	0.87	
Pupilomotor	0.5 ± 0.8	0.6 ± 0.9	0.4 ± 0.7	0.10	0.5 ± 0.9	0.6 ± 1	0.4 ± 0.9	0.25	
Thermoregulatory	2.6 ± 2.7	3.2 ± 2.7	2.2 ± 2.6	0.001	3 ± 2.9	3.4 ± 3.1	2.7 ± 2.7	0.03	

*Adjusted *P*-values (for age, disease duration, and total LED).

Table 4. Gene effects within same gender, disease demographics.

	WOMEN				MEN			
	All	LRRK2-PD	IPD	*P*-value	All	LRRK2-PD	IPD	*P*-value
N (%)	565	254 (44.9)	311 (55.1)		724	276 (38.1)	448 (61.9)	
Age in years (mean ± SD)	65.7 ± 11.4	65.7 ± 11.4	65.7 ± 11.4	0.98	66.1 ± 11.8	65.5 ± 11.8	66.5 ± 11.8	0.28
Age at PD onset (mean ± SD)	57 ± 11.9	55.8 ± 11.2	58 ± 12.4	0.03	57.8 ± 12.3	55.7 ± 11.5	59.1 ± 12.6	<0.001
Age at PD diagnosis (mean ± SD)	60.3 ± 11.2	58.1 ± 11	62.1 ± 11	<0.001	60.7 ± 11.7	56.6 ± 11.6	63 ± 11.1	<0.001
Disease duration in years (mean ± SD)	8.5 ± 6.8	9.5 ± 6.9	7.7 ± 6.6	<0.001	8.2 ± 6.1	9.7 ± 6.3	7.4 ± 5.8	<0.001
LED in mg/d (median, IQR)	375 (700)	417.5 (677)	200 (450)	<0.001	420 (650)	562.5 (760)	375 (615)	<0.001
Family History of PD in first degree relative (*n*, %)	134 (35.5)	78 (45.6)	56 (27.2)	<0.001	133 (26.8)	73 (40.3)	60 (19)	<0.001
Family History of PD in second-degree relative (*n*, %)	62 (17.8)	35 (23.2)	27 (13.6)	0.02	72 (15.4)	35 (21.6)	37 (12.2)	0.007

Nonmotor features

There were no differences in depression scores. Total UPSIT scores were still significantly lower in IPD in the multivariate adjusted model, as also seen in men with *LRRK2* mutations, including UPSIT percentile and proportion of hyposmic subjects (total raw UPSIT score for women with *LRRK2* vs. IPD, 24.4 vs. 21.1, $P = 0.003$). There were no differences in cognitive scores. IPD women had worse RBDSQ scores, but the differences were not significant in the adjusted model (RBDQ 3.3 vs. 5.2, $P = 0.25$). There were no differences in SCOPA-AUT total or subscale scores in the adjusted model.

Table 5. Gene effects within same gender, motor features.

	Women				Men			
	All	LRRK2-PD	IPD	*P*-value*	All	LRRK2-PD	IPD	*P*-value*
UPDRS-I, ON medication (median, IQR)	2 (3)	1 (3)	1 (3)	0.31	0.93	2 (2)	2 (2)	0.67
MDS-UPDRS-II or converted UPDRS_II, ON medication (median, IQR)	11.2 (11.2)	12.3 (14.2)	11 (9.9)	0.99	12.3 (11)	12 (11.3)	12.3 (11)	0.03
MDS-UPDRS-III or converted UPDRS_III, ON medication (mean ± SD)	32.4 ± 19.2	33.2 ± 20.6	31.8 ± 18.1	0.64	32.1 ± 17.1	31.4 ± 17.6	32.5 ± 11.8	0.001
UPDRS-III subscores (mean ± SD)								
Balance/gait	6.1 ± 5.1	6.8 ± 5.7	5.6 ± 4.4	0.93	6.9 ± 4.5	6.9 ± 5.6	6.9 ± 4.5	0.01
Rest tremor	1.4 ± 1.8	1.3 ± 2	1.5 ± 1.7	0.50	1.5 ± 1.8	1.4 ± 1.9	1.5 ± 1.8	0.97
Rigidity	3.5 ± 3	3.7 ± 3.4	3.4 ± 2.6	0.85	4.7 ± 3.5	4.4 ± 3.5	4.8 ± 3.6	0.12
Bradykinesia	7.9 ± 5.6	8.2 ± 6.2	7.7 ± 5	0.81	8 ± 5.6	7.3 ± 5.9	8.3 ± 5.5	<0.001
UPDRS-IV, ON medication (median, IQR)	1 (4.5)	2 (6)	1 (2)	0.049	1 (3)	2 (4.5)	1 (2)	0.67
Asymmetric onset (*n*, %)	298 (86.6)	138 (91.2)	160 (83.8)	0.29	381 (83)	145 (91.8)	236 (78.4)	0.21
Severe L-dopa induced dyskinesias** (*n*, %)	30 (5.6)	18 (7.5)	12 (4.1)	0.05	37 (5.3)	23 (8.8)	14 (3.2)	0.06
Ever present:**								
Bradykinesia	519 (96.1)	223 (95.7)	296 (96.4)	0.37	660 (96.1)	236 (94.8)	424 (96.8)	0.08
Rigidity	488 (90.4)	207 (88.8)	281 (91.5)	0.001	620 (90.2)	220 (88)	400 (91.5)	0.49
Rest Tremor	438 (84.1)	183 (81)	255 (86.4)	0.18	552 (82.3)	203 (84.6)	349 (81)	0.21

*Adjusted *P*-values (for age, disease duration, and total LED.
**Derived from diagnostic check list.

Table 6. Gene effects within same gender, nonmotor features.

	Women				Men			
	All	LRRK2- PD	IPD	*P*-value*	All	LRRK2-PD	IPD	*P*-value*
GDS15 (mean±SD)	5.6 ± 4.3	5.7 ± 4.3	5.6 ± 4.3	0.79	4.7 ± 3.9	5 ± 4	5 ± 3.9	0.19
Total UPSIT score (mean±SD)	23.3 ± 8	24.4 ± 8.2	21.1 ± 7.1	0.003	19.3 ± 7.7	20.9 ± 8	17.2 ± 6.9	<0.001
Hyposmic (*n*, %)	120 (63.2)	72 (55.8)	48 (78.7)	0.01	171 (72.1)	88 (64.7)	83 (82.2)	0.005
Total MoCA score (mean ± SD)	24.6 ± 4.4	24.2 ± 4.5	25 ± 4.3	0.92	24.1 ± 4.3	24.1 ± 4.2	24.1 ± 4.4	0.006
Epworth sleepiness scale total score (mean ± SD)	5.8 ± 5.2	6.5 ± 5.4	5 ± 4.9	0.02	6.3 ± 5.3	6.7 ± 5.4	5.9 ± 5.1	0.34
RBDQ Total (mean ± SD)	3.8 ± 2.7	3.3 ± 2.6	5.2 ± 3.4	0.25	4.1 ± 3	3.6 ± 2.9	5.1 ± 3	0.003
SCOPA-AUT Total score	15.1 ± 10.5	15.1 ± 10.8	15.2 ± 10.1	0.78	13.8 ± 9.2	14 ± 9.5	13.6 ± 8.9	0.44
Gastrointestinal	4.4 ± 3.7	4.2 ± 3.9	4.5 ± 3.4	0.56	4 ± 3.3	4 ± 3.3	4.4 ± 3.5	0.66
Urinary	5.3 ± 4.9	5.6 ± 5.2	5 ± 4.5	0.53	5.7 ± 4.8	5.9 ± 5.2	5.5 ± 4.4	0.88
Cardio	1.4 ± 1.6	1.2 ± 1.7	1.5 ± 1.5	0.76	1 ± 1.5	1 ± 1.5	1.1 ± 1.4	0.28
Pupilomotor	0.6 ± 0.9	0.6 ± 1	0.6 ± 0.9	0.89	0.4 ± 0.8	0.4 ± 0.9	0.4 ± 0.7	0.91
Thermoregulatory	3.3 ± 2.9	3.4 ± 3.1	3.2 ± 2.7	0.36	2.4 ± 2.7	2.7 ± 2.7	2.2 ± 2.6	0.004

*Adjusted *P*-values (for age, disease duration, and total LED). MoCA score is also adjusted by education years.

Gene effects among men

Motor features (Table 5)

Men with G2019S *LRRK2* mutations had slightly lower total MDS-UPDRS-III scores than men with IPD (mean 31.4 vs. 32.5, $P = 0.001$ in the adjusted model), despite having longer disease duration. This finding was primarily driven by lower bradykinesia subscores in mutation carriers (mean 7.3 vs. 8.3, $P < 0.001$). While more *LRRK2*-PD men had asymmetric onset and higher proportion of severe LID, these differences were not significant in the adjusted model (% asymmetric onset 91.7 vs. 78.4, $P = 0.21$; % severe LID 8.8 vs. 3.2, $P = 0.06$).

Nonmotor features (Table 6)

There were no differences in mood scores. MoCA scores were slightly higher among IPD men and significantly different only after adjustment by age, disease duration and education years (24.14 vs. 24.12, $P = 0.006$). Olfaction analysis yielded similar results than in women (mean total UPSIT for men with *LRRK2* men vs. IPD men, 20.9 vs. 17.2, $P < 0.001$). While there were no differences in ESS scores, in the adjusted model, men with IPD had worse RBDSQ scores than *LRRK2*-PD men (mean total score 3.65 vs. 5.14, $P = 0.003$). The difference in RBD between *LRRK2* and IPD appears to be hence driven exclusively by men. There were no differences in total SCOPA-AUT scores, but *LRRK2*-PD men had worse thermoregulatory scores (mean 2.7 vs. 2.2, $P = 0.004$), although the difference magnitude was small.

Discussion

Although genetic determinants may be sexually dimorphic,[21,22] and a specific *LRRK2* gender effect has been postulated,[23] we confirm that the male predominance observed in Western populations with PD is not present in the G2019S mutation in *LRRK2 PD*.[23–25] A higher relative proportion of *LRRK2* carriers among women (45 vs. 55%) vs. men (40 vs. 60%) was observed.[25,26] However, we did not demonstrate a difference between the rates of PD in male and female *LRRK2* mutation carrier PD (52 vs. 48%). This more equal distribution between sexes is not limited to *LRRK2* and is shared by some other genetic forms of PD.[27]

While the percentage of women with IPD with a family history of PD was greater than the percentage of men (27% vs. 19%), because there were overall more men in the IPD group, the absolute number of cases of women ($n = 56$) and men ($n = 60$) with positive family history in the IPD cohort was similar. Taken together, these data suggest a *relatively* greater genetic load in women than men,[26,28] since traditionally male predominance in IPD is not observed in genetic cohorts. This does not mean that the absolute genetic load of PD is greater in women than men. Rather, since PD autosomal dominant genes are transmitted equally to men and women, and these genes appear to be equally penetrant in men and women, they may, however, contribute to a different proportion of PD incidence among the sexes. The greater predominance of PD in men could be attributable to an excess of non-Mendelian deleterious factors or a dearth of protective factors in men. Differential environmental exposures in men and women have been suggested in IPD.[29] Alternatively, women may have similar environmental burden, and/or have greater protection through sexually dimorphic or hormone-mediated influences.[30] Epigenetic factors may also play a role as transcriptomic reports demonstrate downregulation of B-cell-related genes in women with PD compared to those without, as well as men with PD.[31] Differential effects of deleterious factors may play less of a role in *LRRK2* PD, since similar penetrance has been reported in male and female carriers,[25] suggesting that modifiers of penetrance of *LRRK2* PD are not sex-specific, or if they are, are balanced between the sexes.

Through the structure of this study, we were able to examine not only differences between *LRRK2* G2019S mutation PD men and women, but also assess whether these effects were seen in the sex groups in general regardless of gene. We did not find gender differences at age at onset of PD in either group, contrary to previous report by Haaxma et al.[32] and a recent Tunisian study where *LRRK2* women were affected a median 5 years before men.[33] Of interest, men with *LRRK2* mutations were slightly younger than IPD men and had younger age at onset, and although this was not seen in women, supports a *LRRK2*-related effect on age of onset noted in some, but not all studies.

Women with IPD tended to have a more benign motor phenotype, suggested by lower UPDRS-III scores (mainly driven by higher rigidity subscores in men), and also had higher rates of treatment complications (as defined by higher UPDRS-IV scores), despite their overall lower LED, although the effects were not statistically significant using a more stringent significance threshold. While not universal,[34] certain reports suggest a slower disease progression in female patients. A benign phenotype has also been suggested to be related to a more common occurrence of tremor-dominant subtype in women, which in turn has been associated with slower disease progression and less cognitive impairment.[35,36] In our sample, men and women with IPD had similar rates of tremor-dominant subtype (30.3% in IPD women vs. 25.47% in men, $P = 0.59$). Women with LRRK2, however, were less likely

to have a tremor-dominant subtype as compared to LRRK2 men (10.96% in women vs. 33.73%, $P = 0.001$), although the sample size was small. Of interest, whereas the greater predominance of rigidity in men was present in both groups, men also had a worse overall motor UPDRS scores than women in IPD but this was not present in the *LRRK2* men compared to *LRRK2* women. Among women, LRRK2 women were similar to IPD in clinical features but were taking more levodopa.

The most consistent gender-related feature in the literature is lower LED in women.[37,38] Frequently, also increase in dyskinesias in women is reported. In this sample women with IPD and with *LRRK2* PD had lower LED than men form their respective groups, but only differences within IPD were significant. There was a trend toward higher UPDRS IV scores in women in both the *LRRK2* and IPD group, although the prevalence of severe LID did not differ between men and women in either group. This supports a greater presence of medication side effects in women even when adjusted for LED, and independent of a gene effect.

Contrary to other studies, no gender differences were found in mood or cognitive symptoms, daytime sleepiness[39] or RBD in IPD, which may have been due to differences in study design and population. There were mild gender differences in SCOPA-AUT subscores but not in total scores. In men, those with LRRK2 mutations had better olfaction, less RBD, and worse dysautonomia scores. In women, LRRK2 women had better olfaction. UPDRS-I, II, III, and IV were similar among LRRK2 and IPD men, and within LRRK2 and IPD women, with an exception: from the diagnostic check list, LRRK2 women as compared to IPD women had higher proportion of rigidity (ever present).

While the strength of the Michael J Fox Consortium lies in the diversity of study subjects across several continents, by virtue of the multiple sites, there are ethnic, cultural, and treatment differences. One limitation of this analysis is that for subject confidentiality reasons, individual sites and Ashkenazi Jewish status were not available from the dataset and clusters and site effects could not be evaluated. The primary study is also cross-sectional nature, limiting comparisons of progression of disease. We also focused solely on G2019S mutation carriers, as data were most abundant for this group, and it is not clear whether these findings are applicable to other *LRRK2* mutations, or to risk variant groups. We did not focus our analysis on comparing IPD and LRRK2 PD as a group, which has been recently reported using an overlapping sample with ours.[9] We also cannot entirely exclude the possibility that recall bias accounts for some of the observed gender differences, although likely not all. In a previous report on gender differences in LRRK2[26] we argued that the magnitude of the recall bias was unlikely to fully account for the more than twofold difference in the likelihood of having an affected parent among relatives of male and female probands. Finally, there are also limitations in the clinical assessments, such as the assessment of RBD based solely on responses to the RBDSQ questionnaire and not the gold standard, polysomnography.

To conclude, we describe a more "aggressive" phenotype in men with IPD as compared to IPD women and *LRRK2* PD men. Gender differences were less notable in *LRRK2* PD. One potential explanation is that *LRRK2* PD may have a less heterogeneous phenotypic presentation than IPD, and this might mitigate potential sex differences. This study also supports a relative higher genetic load in women with PD, given the larger positive family history rates of PD in IPD women, suggesting greater overall non-Mendelian contribution or possible greater environmental load in men.

While these findings are detected at a population level and are generally small in magnitude, they contribute cumulative data to the genetic counseling of carriers of LRRK2 mutations and may have current clinical implications, for example, the likely higher risk for women to develop motor complications on dopaminergic medication, regardless of genetic etiology. However, more importantly, as the field moves toward personalized medicine and trials are currently underway for specific genetic types of PD, including LRRK2, a better understanding of the variance and gender differences may have implications for sample size and outcome measurements.

In order to parse relative genetic and environmental factors, we recommend that future analyses examine sex differences, including sex-specific focus on environmental factors. Additional measures of progression, including quantitative imaging will also advance our understanding of these sex differences.

Documentation of Author Roles

1 *Research Project*: A. Conception, B. Organization, C. Execution
Marta San Luciano: A, B, C; Robert Ortega: C; Nir Giladi: A, B; Karen Marden: A, B; Susan Bressman: A, B; Rachel Saunders-Pullman: A, B,C.

2 *Statistical Analysis*: A. Design, B. Execution, C. Review, and Critique
Marta San Luciano: A, B, C; Cuiling Wang: A, B, C; Robert Ortega: B, C; Nir Giladi: C; Karen Marden: C; Susan Bressman: C; Rachel Saunders-Pullman: A, C.

3 *Manuscript Preparation*: A. Writing of the first draft, B. Review, and Critique
Marta San Luciano: A; Cuiling Wang: B; Robert

Ortega: B; Nir Giladi: B; Karen Marden: B; Susan Bressman: B; Rachel Saunders-Pullman: B.

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Conflict of Interest

None of the authors have relevant potential conflicts of interest to report related to this work.

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