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Sex differences in LRRK2 G2019S and idiopathic Parkinson’s Disease

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Study supported by NIH K02 NS073836 (RSP), the Michael J 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.
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). Data from the July 2014 data cut were utilized. A total of 1289 cases with PD, including 530 LRRK2 PD carriers and 759 non-carrier 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-UPDRS11 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, BDI15), dysautonomia (SCOPA-AUT,16), olfaction (UPSIT17), and sleep (Epworth Sleepiness Scale, ESS18 and REM sleep behavior disorder questionnaire, RBDSQ19). 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 PD 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.

**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. 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
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.

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

|                  | All  | Women | Men  | \( P \)-value | All  | Women | Men  | \( P \)-value |
|------------------|------|-------|------|--------------|------|-------|------|--------------|
| N (%)            | 759  | 311 (41) | 448 (59) | 0.36        | 530  | 254 (47.9) | 276 (52) | 0.86         |
| Age in years     | 66.17 \( \pm \) 11.7 | 65.7 \( \pm \) 11.4 | 66.5 \( \pm \) 11.8 | 0.36 | 65.6 \( \pm \) 11.6 | 65.7 \( \pm \) 11.4 | 65.5 \( \pm \) 11.8 | 0.36 |
| Age at PD onset   | 58.7 \( \pm \) 12.5 | 58 \( \pm \) 12.4 | 59.1 \( \pm \) 12.6 | 0.24 | 55.7 \( \pm \) 11.3 | 55.8 \( \pm \) 11.2 | 55.7 \( \pm \) 11.4 | 0.95 | <0.001 |
| Age at PD diagnosis | 62.7 \( \pm \) 11.1 | 62.1 \( \pm \) 11 | 63 \( \pm \) 11.1 | 0.39 | 57.3 \( \pm \) 11.4 | 58.1 \( \pm \) 11 | 56.6 \( \pm \) 11.6 | 0.24 | <0.001 |
| Disease duration in years (mean \( \pm \) SD) | 7.5 \( \pm \) 6.1 | 7.7 \( \pm \) 6.6 | 7.4 \( \pm \) 5.8 | 0.93 | 9.6 \( \pm \) 6.7 | 9.5 \( \pm \) 6.9 | 9.7 \( \pm \) 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 |

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

|                      | IPD All | IPD Women | IPD Men | P-value* | LRRK2-PD All | LRRK2-PD Women | LRRK2-PD 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 All | IPD Women | IPD Men | P-value* | LRRK-PD All | LRRK-PD Women | LRRK-PD 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 (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     |

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

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

|                  | WOMEN All | LRRK2-PD | IPD | P-value | MEN All | LRRK2-PD | IPD | P-value |
|------------------|-----------|----------|-----|---------|---------|----------|-----|---------|
| N (%)            | 565       | 254 (44.9) | 311 (55.1) | 0.98 | 724      | 276 (38.1) | 448 (61.9) | 0.28 |
| 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 (RBDSQ 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          | 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) & 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 |
| & & 488 (90.4) | 207 (88.8) | 281 (91.5) | 0.001 | 620 (90.2) | 220 (88) | 400 (91.5) | 0.49 |
| & & 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          | 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 |
| Pupillomotor | 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 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, and a specific LRRK2 gender effect has been postulated, we confirm that the male predominance observed in Western populations with PD is not present in the G2019S mutation in LRRK2 PD. A higher relative proportion of LRRK2 carriers among women (45 vs. 55%) vs. men (40 vs. 60%) was observed. 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.

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, 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. Alternatively, women may have similar environmental burden, and/or have greater protection through sexually dimorphic or hormone-mediated influences. 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. 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, 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. and a recent Tunisian study where LRRK2 women were affected a median 5 years before men. 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, 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. 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, \( P = 0.59 \)).
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.\textsuperscript{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\textsuperscript{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.\textsuperscript{7} 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\textsuperscript{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
   
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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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