RESEARCH ARTICLE

Differences in Sex-Specific Frequency of Glucocerebrosidase Variant Carriers and Familial Parkinsonism

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ABSTRACT: Background: Although men and women with the *LRRK2* G2019S variant appear to be equally likely to have Parkinson's disease (PD), the sex-distribution among *glucocerebrosidase* (*GBA*) variant carriers with PD, including limited to specific variant severities of *GBA*, is not well understood. Further, the sex-specific genetic contribution to PD without a known genetic variant is controversial.
Objectives: To better understand sex differences in genetic contribution to PD, especially sex-specific frequencies among *GBA* variant carriers with PD (*GBA* PD) and *LRRK2*-G2019S variant carriers with PD (*LRRK2* PD).
Methods: We assess differences in the sex-specific frequency in *GBA* PD, including in subsets of *GBA* variant severity, *LRRK2* PD, and idiopathic PD in an Ashkenazi Jewish cohort with PD. Further, we expand prior work evaluating differences in family history of parkinsonism.
Results: Both idiopathic PD (267/420 men, 63.6%) ($P < 0.001$) and *GBA* PD overall (64/107, 59.8%) ($P = 0.042$) were more likely to be men, whereas no difference was seen in *LRRK2* PD (50/99, 50.5%) and *LRRK2*/*GBA* PD (5/10, 50%). However, among *GBA* PD probands, severe variant carriers were more likely to be women (15/19 women, 79.0%) ($P = 0.005$), whereas mild variant carriers (44/70 men, 62.9%) ($P = 0.039$) and risk-variant carriers (15/17 men, 88.2%) ($P = 0.001$) were more likely to be men.
Conclusions: Our study demonstrates that the male-sex predominance present in *GBA* PD overall was not consistent across *GBA* variant severities, and a female-sex predominance was present among severe *GBA* variant carriers. Therefore, research and trial designs for PD should consider sex-specific differences, including across *GBA* variant severities. © 2022 International Parkinson and Movement Disorder Society.

Key Words: GBA; LRRK2; Parkinson's; sex; family history

Introduction

There is a consistent sex discrepancy in the prevalence of Parkinson's disease (PD),[1-4] with disease occurring ~1.4 times more frequently in men.[5] Differences in sex-related frequencies are not well understood, nor are the differential contributions of protective and deleterious factors between men and women.[6-17] These include longer exposure to potentially protective endogenous or exogenous sex hormones in women.[11-15] It has been postulated that men have a higher relative contribution of non-genetic risk factors than women,[7] including greater exposure to occupational environmental toxins.[8] Differences may also be attributable to sex-specific genetic factors.[18,19] However, evaluation of genome-wide association studies (GWAS) data did not identify disparate heritability

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estimates of autosomal dominant loci between men and women with PD,[20] and data are conflicting regarding whether family history is increased in women with PD.[7,21,22]

Differences in sex-related frequency of disease occur in some, but not all genetic forms of PD, and this may depend not only on the gene, but also the particular variant.[23] However, the evidence is not consistent across studies, including across separate meta-analyses. For example, the male/female ratio in PD associated with the *LRRK2* G2019S variant (*LRRK2* PD) consistently approximates 50:50.[15,21,24-27] A landmark meta-analysis evaluating men and women carrying *LRRK2* variants overall, and separately by G2019 and G2385 variants, demonstrated that both sexes shared similar odds for developing PD, lending support to the hypothesis that the genetic load in *LRRK2* PD outweighs sex-specific protective or deleterious factors.[28] A follow-up meta-analysis studying sex differences in *LRRK2* PD demonstrated a higher prevalence of PD in women carrying *LRRK2* variants that was attributed to the G2019S variant, but not the G2385 variant.[29] The distribution of sex in PD associated with *glucocerebrosidase* (*GBA*) variants (*GBA* PD), the leading genetic contributor to PD, is controversial. Although most have shown a male predominance, or more equal sex distribution, a subsequent meta-analysis demonstrated a higher prevalence of women among *GBA* PD in North America and Europe, but not in Asia or Oceana.[30-32,33] It has separately been suggested that the sex distribution in *GBA* PD may also vary depending on the specific *GBA* variant under study.[23]

To better understand sex differences in genetic contribution to PD and among genetic subgroups, we assess the sex distribution among carriers of *GBA* variants and/or *LRRK2* G2019S, as well as potential gene associated sex differences in family history in a cohort comprising *GBA* PD, *LRRK2* PD, and PD without genetic variants.

Methods

Subjects

Consecutive probands with PD who reported Ashkenazi Jewish ancestry were invited to a study of genetics of Parkinson research at Mount Sinai Beth Israel/Mount Sinai (New York, USA), including a subset previously reported.[7] Participants provided written informed consent, and the study was approved by the Institutional Review Board.

All participants were genotyped for *LRRK2* G2019S and the 11 most common GBA variants in the Ashkenazi Jewish population (N370S, L444P, 84GG, IVS2 + 1, V394L, D409H, A456P, R496H, RecNciI, E326K, and T369M,) using the Tag-It Mutation Detection Kit (Luminex Molecular Diagnostics, Toronto, ON, Canada) according to the manufacturer's instructions. Multiplex polymerase chain reaction was used to amplify the regions around the target genes. These regions were subjected to allele-specific primer extension, hybridized to specific Luminex beads via Universal Tags, and sorted on a Luminex 100 IS platform (Luminex Corporation, Austin, TX, USA). Genotyping was then completed using the Tag-It Data Analysis Software (Luminex Molecular Diagnostics), and as previously described.[34-36]

Family history of parkinsonism in first-degree relatives of probands was determined by self-report through family history screen (standardized family history questionnaire or clinical research screen) or by pedigree review.[7]

Data Sharing

Data requests from qualified investigators for purposes of replicating procedures and results can be made to the corresponding author for a subset of de-identified data, for which consent for sharing was obtained.

Analysis

Differences in sex distribution, in the cohort overall, and in probands based on their *LRRK2* G2019S and *GBA* variant status, were determined using one-sample tests of equality of proportions. Odds-ratios were estimated using logistic regression for the association between reported sex and genetic status. *GBA* variants were subcategorized into three groups based on the variant "severity" and the association between the *GBA* variant and Gaucher disease (GD), as severe (when biallelic causing neuronopathic GD [84GG, IVS2 + 1, L444P, RecNcil, V394L]), mild (associated with GD type 1 when biallelic mild or together with a severe variant [N370S, R496H]), and risk-variant (not causing GD when biallelic, [E326K, T369M]).[37] Screening did not detect any carriers of *GBA* D409H, and *GBA* A456P was only present among RecNcil carriers. To determine whether family history of parkinsonism in first-degree relatives differed by sex overall, and separately based on *LRRK2* and *GBA* variant status, sex-specific history of parkinsonism in a first-degree relative was analyzed using unadjusted logistic regression to estimate odds ratios (ORs) and standard errors, as well as adjusted for proband age at time of family history collection and age at onset of PD. A sensitivity analysis limited to the history of parkinsonism in a parent was also performed. All analyses were performed using Stata statistical software version 16 (StataCorp, TX).

Results

Demographic, clinical and family history in first-degree relatives was available for 636 probands with PD, including: 420 idiopathic PD, 99 *LRRK2* PD,

107 *GBA* PD, and 10 *LRRK2/GBA* PD. Among the 636 PD probands, 250 were women (39.3%) compared with 386 men (60.7%). Family history was obtained by family history screen (n = 454) and pedigree review (n = 182). A total of 609 of the probands had complete information for the adjusted analysis.

Sex Distribution

Sex Distribution within Groups

Both idiopathic PD (267/420 men, 63.6% men, $P < 0.001$) and *GBA* PD overall (64/107 men, 59.8%, $P = 0.042$) were more likely to be men. In contrast, there was no difference in sex-specific distribution in *LRRK2* PD (50/99 men, 50.5%) ($P = 0.920$) and *LRRK2/GBA* PD (5/10 men, 50%) ($P = 1$).

However, among *GBA* PD probands, severe *GBA* variant carriers were more likely to be women (15/19 women, 79.0% women, $P = 0.005$), whereas it was the reverse association with mild *GBA* variant carriers (44/70 men, 62.9% men, $P = 0.039$), and variant *GBA* carriers (15/17 men, 88.2% men, $P = 0.001$), who were both more likely to be men.

Sex Distribution between Groups

A greater proportion of *LRRK2* were women compared with idiopathic PD (*LRRK2* PD vs. idiopathic PD 49.5% vs. 36.4, $P = 0.017$), and *GBA* PD (*LRRK2* vs. *GBA* 49.5% vs. 40.2%, $P = 0.18$), though the latter comparison was not statistically significant (Table 1, Fig. 1).

Odds ratios comparing *GBA* PD to idiopathic PD and *LRRK2* PD, and separately comparing categories of *GBA* variants to each other, idiopathic PD and *LRRK2* PD are shown in Table 2.

Of note, severe *GBA* variant carriers were more likely to be women than idiopathic PD (OR [95% confidence interval (CI)] = 6.54 [2.13–20.07], $P = 0.001$), *LRRK2* PD (3.83 [1.19–12.34], $P = 0.025$), as well as mild *GBA* variant carriers (6.35 [1.90–21.17], $P = 0.003$) (Table 2).

Family History of Parkinsonism

Among idiopathic PD, female probands were more likely to report a family history of parkinsonism in a first-degree relative compared to male probands (22.5% of women vs. 15.4% of men) (OR Standard error [SE] = 1.70 (0.43), $P = 0.038$) (Fig. 2). In the genetic forms, there was no difference in the likelihood to report a family history of parkinsonism in a first-degree relative between men and women: among *LRRK2* PD (40.8% of women vs. 30.6% of men, OR [SE] = 1.23 [0.51], $P = 0.622$), *GBA* PD (18.6% of women vs. 18.8% of men, OR [SE] = 0.99 [0.50], $P = 0.985$), or *LRRK2/GBA* PD (20.0% of women vs. 40.0% of men, OR [SE] = 0.38 [0.54], $P = 0.497$). There was also no difference when separately subdividing *GBA* PD by the severity of variants. All results were maintained when adjusting for proband age at time of family history collection and age at onset of PD.

Because the penetrance of PD associated variants increases with age,[30] and siblings are younger and less likely to have reached older ages than the parents, we performed a sensitivity analysis limiting the history of parkinsonism to the parents of the probands. Results from the overall model were maintained such that among idiopathic PD, women were more likely to report a family history of parkinsonism in a parent compared to men (19.6% vs. 11.6%, OR (SE) = 1.86 (0.52), $P = 0.027$). There was no difference found between men and women in the likelihood of parkinsonism in a parent among *LRRK2* PD (28.6% vs. 32.0%, OR [SE] = 0.85 [0.37], $P = 0.711$), *GBA* PD (11.6% vs. 14.1%, OR [SE] = 0.80 [0.48], $P = 0.715$), or *LRRK2/GBA* PD (20.0%

TABLE 1 *Summary of sex distribution among each major PD group, and separately among GBA-variant severities*

Cohort	N	Women, No. (% cohort)	Men, No. (% cohort)	*P*-value
Among PD groups				
Idiopathic PD	420	153 (36.4)	267 (63.6)	<0.001
LRRK2 PD	99	49 (49.5)	50 (50.5)	0.920
LRRK2/GBA PD	10	5 (50.0)	5 (50.0)	1.00
GBA PD	107	43 (40.2)	64 (59.8)	0.042
Among GBA-variant severities				
Severe *GBA* PD	70	15 (79.0)	4 (21.1)	0.005
Mild *GBA* PD	107	26 (37.1)	44 (62.9)	0.377
Risk-variant *GBA* PD	17	2 (11.8)	15 (88.2)	0.002

Within group summary of sex distribution in PD overall and in the different genetic groups. Although idiopathic PD and *GBA* PD are more likely to be men, *LRRK2* PD and *LRRK2/GBA* PD were not. Further, carriers of a severe *GBA* variant were more likely to be women, unlike carriers of a mild *GBA* variant, who were more likely to be men. PD: Parkinson disease; LRRK2 PD: PD associated with the *LRRK2* G2019S variant; *LRRK2/GBA* PD: PD associated with the *LRRK2* G2019S variant and with glucocerebrosidase (*GBA*) variants; GBA PD: PD associated with GBA variants

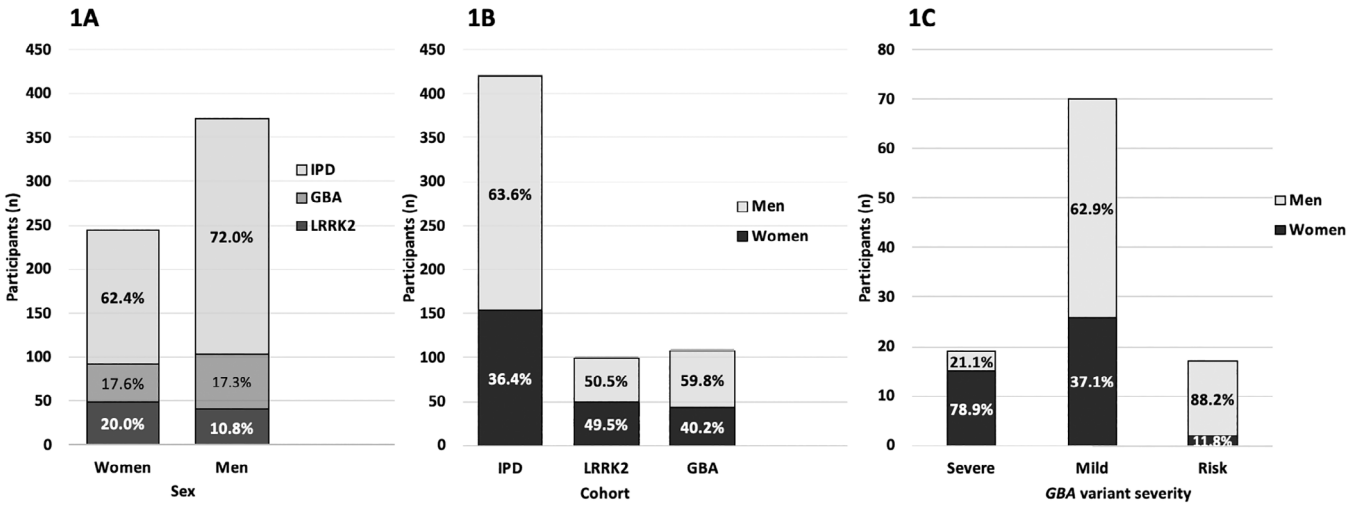

FIG. 1. Sex distribution of Parkinson's disease (PD) overall and in idiopathic Parkinson's disease (IPD), *LRRK2* and *glucocerebrosidase (GBA)*, including by *GBA* variant. (**A**) Comparison of the frequency of LRRK2 and GBA variants (overall) among men and women. Note the greater proportion of women versus men with *LRRK2* PD (20% vs. 10.8%), similar proportion of *GBA* PD in both (17.6% vs. 17.3%), and subsequent smaller proportion of idiopathic PD comprising women vs men (62.4% vs. 72.0%) ($P = 0.057$). (**B**) Distribution of sex by PD groups. Note, the overall greater percentage of men with *GBA* PD versus women with *GBA*-PD ($P = 0.042$), unlike *LRRK2* PD ($P = 0.920$), and similar to IPD ($P < 0.001$) (**C**) Sex frequency in *GBA*-PD separated by variant severity, as defined by severe, mild or risk-variant.[37] *GBA* variants include the major variants (both severe and mild variants), which, when biallelic decrease activity of the GBA enzyme and cause Gaucher disease (GD), but when monoallelic increase the risk of synucleinopathies including PD, PD with dementia (PD-D), and dementia with Lewy bodies (DLB); and risk-variants, which when biallelic, do not cause Gaucher disease, but are associated with increased risk of PD and DLB.[37,56,73] Similar to (**B**) where *GBA* variants overall are associated with greater risk in men, there is significant increase in men with mild variants and risk-variants. In stark contrast, however, there is greater frequency of severe variants in women ($P = 0.001$).

vs. 40.0%, OR [SE] = 0.38 [0.54], $P = 0.497$). Last, although idiopathic PD were more likely to report a history of parkinsonism in a father (43/61, 70.5%) compared to a mother (19/61, 31.2%) ($P = 0.002$), there was no difference in maternal or paternal risk of parkinsonism among *LRRK2* PD or *GBA* PD (Table 3).

No difference in age at onset was found between men and women in any PD group. Similarly, proband age at time of family history collection was not different between men and women ($P = 0.443$).

Discussion

Our study demonstrates that although male-sex predominance was present in *GBA* PD overall, it was not consistent across *GBA* variant types and was even reversed for severe variants. This supports that sex differences in *GBA* PD may be variant dependent.[23] Most surprising was our finding that severe-*GBA* variant carriers were most likely to be women (15/19), whereas mild-*GBA* variant carriers and *GBA* risk-variant carriers (comprised of E326K and T369M carriers) were more likely to be men (15/17). We also replicated most previous reports demonstrating a greater frequency of men in *GBA* PD overall when considering all *GBA* variants together,[33,38] although some have also shown that *GBA* PD may have similar sex ratios between men and women,[30-32] or even greater frequency of women among certain risk variants.[39]

To better address the impact of sex on PD prevalence in genetic subtypes, meta-analyses, including in both Ashkenazi Jewish and non-Ashkenazi Jewish populations, as well as a diversity of mutation types, are necessary. Our study may be divergent from other studies for several reasons. Heterogeneity in cohorts and the frequency of genotypic variants across different ethnic groups,[40,41] as well as differences in *GBA* screening methods, may have contributed to the diverse reporting of sex distribution in *GBA* PD overall.[28] European cohorts are more likely to have a greater proportion of severe variant carriers than, for example, Ashkenazi Jewish cohorts in whom the mild variants are most frequent.[42,43] *GBA* screening methodologies, notoriously difficult because of a pseudogene, have changed over time, as has our knowledge of variants considered pathogenic.[44] Case ascertainment decisions, specifically whether variant cases (ie, *GBA* E326K and *GBA* T369M) are included as *GBA* PD, or excluded as GBA dementia with Lewy bodies (DLB), for example, and clinical characteristics, such as whether subjects with primarily dementia versus PD are screened, may lead to significant cohort differences including sex-related differences. Although we did not have systematic data on dementia in family members, our finding that the male sex predominance varied across *GBA* variant types suggests that the population studied and *GBA* variants screened likely contribute to some of the phenotypic heterogeneity. A recent meta-analysis in *GBA* carriers suggests men are more likely to develop DLB compared to women (OR, [95% CI] = 1.60 [0.93, 2.74]), although the increase was not

TABLE 2 *Regression analysis of sex distribution among each major PD group and separately among* GBA-*variant severities*

Cohort	OR (95% CI)	*P*-value
Model comparing odds of being a woman among PD groups		
LRRK2 PD vs. idiopathic PD	1.71 (1.10–2.66)	0.017
LRRK2 PD vs. *LRRK2/GBA* PD	0.98 (0.27–3.60)	0.976
LRRK2/GBA PD vs. idiopathic PD	1.75 (0.50–6.12)	0.385
GBA PD vs. idiopathic PD	1.17 (0.76–1.81)	0.473
GBA PD vs. *LRRK2* PD	0.69 (0.39–1.19)	0.180
GBA PD vs. *LRRK2/GBA* PD	0.67 (0.18–2.46)	0.548
Model comparing odds of being a woman including GBA-variant severities		
Severe *GBA* PD vs. idiopathic PD	6.54 (2.13–20.07)	0.001
Severe *GBA* PD vs. *LRRK2* PD	3.83 (1.19–12.34)	0.025
Severe *GBA* PD vs. *LRRK2/GBA* PD	3.75 (0.71–19.71)	0.118
Severe *GBA* PD vs. mild *GBA* PD	6.35 (1.90–21.17)	0.003
Severe *GBA* PD vs. risk-variant *GBA* PD	28.12 (4.46–177.46)	<0.001
Mild *GBA* PD vs. idiopathic PD	1.03 (0.61–1.74)	0.909
Mild *GBA* PD vs. *LRRK2* PD	1.66 (0.88–3.10)	0.112
Mild *GBA* PD vs. *LRRK2/GBA* PD	0.59 (0.16–2.24)	0.439
Mild *GBA* PD vs. risk-variant *GBA* PD	4.43 (20.94–0.94)	0.060
Risk-variant *GBA* PD vs. idiopathic PD	0.23 (0.05–1.03)	0.055
Risk-variant *GBA* PD vs. *LRRK2* PD	0.14 (0.03–0.92)	0.010
Risk-variant *GBA* PD vs. *LRRK2/GBA* PD	0.13 (0.02–0.92)	0.040

Two models estimating odds ratios, comparing odds of being a woman between groups. As was expected, *LRRK2* PD were more likely to be women than idiopathic PD (OR, SE: 1.71, 1.10–2.66; $P = 0.017$). Although the odds of being a woman were not different between *GBA* PD and idiopathic PD (OR, SE = 1.17, 0.76–1.81; $P = 0.473$) or *GBA* PD and *LRRK2* PD (OR, SE = 0.69, 0.39–1.19; $P = 0.180$), severe *GBA* PD were more likely to be women than both idiopathic PD (6.54, 2.13–20.07; $P = 0.001$), *LRRK2* PD (3.83, 1.19–12.34; $P = 0.025$), and even mild *GBA* PD (6.35, 1.90–21.17; $P = 0.003$). PD: Parkinson disease; LRRK2 PD: PD associated with the *LRRK2* G2019S variant; *LRRK2/GBA* PD: PD associated with the *LRRK2* G2019S variant and with glucocerebrosidase (*GBA*) variants; GBA PD: PD associated with GBA variants

statistically significant ($P = 0.09$).[45] To better discern risk-specific sex differences in these sub-groups, inclusion of participants with PD dementia and DLB in future study is warranted. Alternatively, our sex difference may be because of chance and sample size.

The intriguing finding of female predominance among severe *GBA* carriers will be most important if replicated in further work, but merits discussion as the sex differences in PD are poorly understood. The finding raises questions about possible pathophysiologic differences in expression of the variants.[46,47] Severe variants confer the greatest genetic risk of *GBA* related PD because they have higher penetrance, as well as earlier age of onset.[37,48] As such, one might postulate there would be fewer male/female differences. Indeed, this is the case for *LRRK2* PD, which has a higher penetrance than mild variant or risk-variant *GBA*, approximating 25% by the age of 80 and no sex-related differences in penetrance.[49] We speculate that the sex ratio reversal we observed for severe-*GBA* variants could be a consequence of a difference in disease expression, but one that encompasses not only PD, but DLB. The spectrum of *GBA* related synucleinopathy may be thought of as ranging from DLB with particularly early cortical Lewy body deposition, to PD with dementia (PD-D), with cortical Lewy bodies later in the clinical course, to the mildest, PD, with a lower cortical Lewy body burden.[23,31,50-54] We propose that men with severe variants may be more likely to develop DLB, with more widespread cortical pathology, whereas those with mild and risk variants, will more often develop PD-D and PD. In contrast, the women with severe *GBA* variants may be more likely to develop PD-D and PD, whereas women with mild and risk-variant variants may be slightly less likely to develop PD than men.

Support for this sex-related differential expression hypothesis includes the observations that *GBA* variants are also the leading genetic risk factor for DLB, sex-related differences in *GBA* variants have been observed both in *GBA* PD and *GBA*-related DLB,[23] and there is a propensity for dementia and more widespread synuclein pathology in men.[55] There is also greater risk for dementia in male *GBA* carriers with parkinsonism, including carriers of the severe *GBA* variant, L444P.[23] Further, in one pathologic and clinical study of DLB, *GBA* variants were present in 36% of pure DLB cases, and the great majority (90%) of *GBA* variant carriers were men.[56] It is therefore possible that our findings point not to the lack of expression of severe *GBA* variants in men, but to a varied phenotype of DLB rather than PD. Hence, the "missing" severe *GBA* carriers may not be controls, but rather may have DLB, and the sex-differences described in our study may reflect the preferential sampling of parkinsonism patients (PD and PD-D) from our movement disorders clinic. It is likely that DLB and severe PD-D would instead have

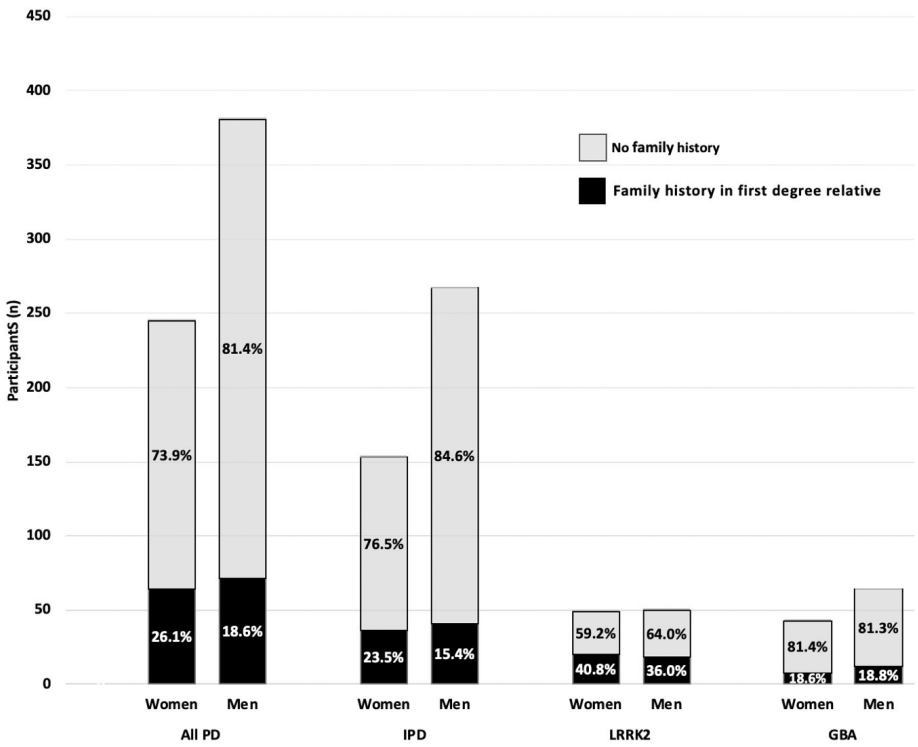

FIG. 2. Proportion of participants, overall and by PD group, with a family history of PD, stratified by sex. As the black signifies individuals with parkinsonism in a first-degree relative, the grey area nonetheless includes a subset that likely have a major genetic contribution that is yet to be determined. As anticipated, because of lower penetrance in *GBA* PD compared to *LRRK2* PD, the proportion with first degree family member with parkinsonism is greater in the *LRRK2* PD (38.4%) than *GBA* PD (18.7%) ($P = 0.002$). Because a smaller proportion of men have a first-degree family history of parkinsonism, there is a larger contribution of other factors including additional genetic, epigenetic, environmental, hormonal and structurally different factors.[19,68,69] We cannot exclude that there is also an undetermined "protective factor" portion that is also responsible for the smaller percentage of non-first-degree family member cases in the women. We postulate that the differential lipid response to inflammation that may be responsible for sex differences in GBA variant PD may play a role in idiopathic PD as well.[57-61]

TABLE 3 *Differences in reported history of paternal and maternal parkinsonism between PD groups*

	Parkinsonism in parent, No. (%)	Parkinsonism in mother, No. (%)	Parkinsonism in father, No. (%)	*P*
Idiopathic PD	61/420 (14.5)	19/61 (31.2)	43/61 (70.5)	0.002
LRRK2 PD	30/99 (30.3)	16/30 (53.3)	16/30 (53.3)	1
GBA PD	14/107 (13.1)	5/14 (35.7)	9/14 (64.3)	0.268
LRRK2 GBA PD	3/10 (30.3)	2/3 (66.7)	1/3 (33.3)	0.531

Although idiopathic PD were more likely to report a history of parkinsonism in a father (43/61, 70.5%) compared to a mother (19/61, 31.2%) ($P = 0.002$), there was no difference in maternal or paternal risk of parkinsonism among *LRRK2* PD or *GBA* PD. PD: Parkinson disease; LRRK2 PD: PD associated with the *LRRK2* G2019S variant; *LRRK2*/*GBA* PD: PD associated with the *LRRK2* G2019S variant and with glucocerebrosidase (*GBA*) variants; GBA PD: PD associated with GBA variants

presented to the cognitive/behavioral clinic. Had we also evaluated DLB patients, we may have found that the male severe *GBA* variant carriers clustered in the DLB cohort. However, we did not include DLB in our cohort, and to test this hypothesis, future studies are needed that systematically recruit both DLB and PD.

Further, others have reported sex differences that depend on the particular variant, but in a different direction than ours.[23] Straniero et al,[23] found that the *GBA* T369M carriers in their DLB cohort were more likely to be women, whereas in our sample, probands carrying a *GBA* T369M variant were more likely to be men (7/7 *GBA* PD, 100%). This highlights that to determine the validity of our hypothesis it will be important not only to look at variant severity but at the sex distribution among *GBA* PD with severe, mild, and risk-variant *GBA* variants.

The etiology of sex differences in *GBA* PD, and idiopathic PD as well, might be attributable in part to sexual dimorphism in sphingolipid metabolism, inflammation, and microgliosis, as well as the more widely studied differences in distribution of environmental and hormonal

factors.[57-61] These factors may play a role in idiopathic PD without *GBA* variants or may be exaggerated in those harboring *GBA* variants. As *GBA*-related effects may be mediated, at least in part by substrate accumulation of sphingolipids,[62] we postulate that women may be less vulnerable to the additional sphingolipid accumulation than men.

Further, because GBA activity may be decreased in idiopathic PD,[63] a group that also has a greater predominance of men, our study raises the question as to whether sex-related differences in sphingolipids and lipid metabolism might play a role not only in *GBA* related parkinsonism, but in idiopathic PD as well. Estrogen may also modulate lipid rafts and preserve neuronal membrane lipids.[64] Further, sex has an effect on monocyte gene expression in PD,[57] with greater inflammatory response to lipopolysaccharide in women with PD and overall enhanced expression of interleukin 6, TNF-α, and interleukin 1β in astrocytes in response to lipopolysaccharide stimulation.[65] Several lines of evidence support that sex-hormones may also mediate the microglia response, and the differential immune response could, therefore, mediate sex-dependent effects of inflammation.[61,66,67] Therefore, the degree to which lipid changes are associated with specific *GBA* variants and present in non-*GBA* variant PD warrants further examination.

As predicted, our study confirms that the male predominance of PD is lost in *LRRK2* G2019S carriers compared with idiopathic PD.[21,24,25,27] This is in line with most other studies of major *LRRK2* variants and further supports that the genetic contributions in *LRRK2* G2019S carriers outweighs other sex-related factors associated with development of disease.

Finally, in this larger follow-up analysis we continue to demonstrate that a greater proportion of women with idiopathic PD report family history of PD, leading us to postulate that the relative contribution of "extra-genetic" factors is greater among men than women (Fig. 2). This is consistent with some,[7,21] but not all prior studies. These "extra-genetic" factors may include epigenetic influences, as well as environmental, hormonal, and other contributors.[10,19,69]

Our cohort has several limitations. Our sample size was smaller than others, and we did not have complete GBA sequencing. However, because we limited our cohort to Ashkenazi Jews and were able to ascertain the major *GBA* variants in this population, it is likely that only a few additional *GBA* cases were missed.[70] Additionally, because we limited our analysis to the *LRRK2* G2019S variant, we cannot evaluate the sex-related effect that might be seen with other *LRRK2* variants. Further, for our investigation of family history in first-degree relatives, multiple sources of information (pedigree vs. family history screen) were used to determine the proband's family history of parkinsonism. However, in sensitivity analyses adjusting for information source, all significant findings remained. We were also not able to clinically confirm the reported diagnosis of parkinsonism in many first-degree relatives. We also cannot exclude that the greater family history seen in female probands compared to male probands is explained by a sex-specific, differential recall bias of PD in a family member,[71] although whether a sex-specific differential recall of family history of PD exists has not been consistently shown,[72] and our study supports previous reports of a greater family history in women compared to men.[7,21] Last, it is a limitation that our results may not be generalizable to other populations, particularly those with different founder effects.

Conclusion

Our study highlights sex-related differences in PD, suggesting a proportionally greater non-genetic risk in men that appears to explain much of the sex difference, as well as a postulated sex-related expression difference in phenotype relative to *GBA* variants. As variants in *GBA* constitute the leading genetic etiology of PD and DLB, and clinical trials addressing *GBA* have begun, it will be essential to consider sex related differences in trial design, including allocation schema to treatment and placebo arms. Further study, including meta-analysis in Ashkenazi Jewish and non-Ashkenazi Jewish cohorts continues to be warranted. ■

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Data Availability Statement

Data Sharing: Data requests from qualified investigators for purposes of replicating procedures and results can be made to the corresponding author for a subset of de-identified data, for which consent for sharing was obtained.

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Author Roles

(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.

R.A.O.: conception, statistical analysis, draft of manuscript, editing of final version of the manuscript.
S.B.B.: execution, review and critique, editing of final version of the manuscript.
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