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Gender differences in the risk of familial parkinsonism: beyond LRRK2?

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Abstract

Background—G2019S mutations in the *LRRK2* gene are responsible for up to 18% of PD in individuals of Jewish descent. While a male preponderance of Parkinson disease (PD) has been consistently reported, this gender difference is not noted in *LRRK2* G2019S mutation carriers.

Methods—In order to test whether there is an increased genetic component in women of Jewish background in general, we examined family history of parkinsonism in 175 Jewish PD patients (82 female and 93 male) and assessed whether parkinsonism was more frequent in family members of women with PD in comparison with family members of men with PD, adjusting for *LRRK2* G2019S mutations in the proband.

Results—Using Cox proportional hazards models to evaluate the risk of parkinsonism among family members of PD subjects, having a daughter with PD compared with a son was associated with increased risk of parkinsonism in the parent (HR 2.59, p=0.014) as was having a child with a *LRRK2* G2019S mutation (HR 3.19, p=0.003). The increased risk among parents of women with PD persisted when adjusting for *LRRK2* status (HR 2.19, p=0.023).

Conclusion—Among individuals of Jewish descent, there is a relatively greater genetic load in women with PD, and this is not fully accounted for by the G2019S mutation. Further study that evaluates family information bias and assesses the role of glucocerebrosidase mutations is indicated.

Keywords

Parkinson Disease; women; gender; LRRK2; Jewish; family history; genetic

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Introduction

In Western populations, men are approximately 1.5 times more likely to develop Parkinson disease (PD) than women [4,12,29,32]. However, among cases with the *LRRK2* G2019S mutation, the male gender predominance is not present [17]. The etiology of the male preponderance of PD is unknown but might be attributed to a greater influence of deleterious factors compared with protective factors. Environmental pathogens, such as work related exposure to toxins, may be more frequent in the male work environment and may increase the incidence of PD in men [2]. Men also do not benefit from putative protective factors, such as early life exposures to endogenous estrogen and progesterone [reviewed by 9, 20, 25, 33]. Further, there may also be gender related differences in expression of genes related to PD pathways [28].

In contrast, for most autosomal dominant disorders, such as *LRRK2* related PD, penetrance is similar in men and women as genetic risks are equally transmitted to both sexes [13,22,30]. We hypothesize that the relative causal contributions in men and women differ; that because women may have less overall deleterious exposures compared to men, women who develop PD will have a relatively increased rate of genetic PD, manifested as higher frequency of positive family history of parkinsonism, and this may in part be responsible for the relatively higher frequency of *LRRK2* mutations among Ashkenazi women with PD than men with PD. We examined family history of parkinsonism in female and male probands from an ongoing genetic study of Jewish PD patients and tested whether parkinsonism in first-degree relatives was more frequent in family members of women with PD in comparison with family members of men with PD.

Materials and Methods

We studied family history and clinical features in 177 patients with Parkinson's disease who self-identified as Jewish, and participated in a genetic study of PD at the Department of Neurology at Beth Israel Medical Center in New York City. Movement disorder specialists performed clinical assessments, and all subjects met strict diagnostic criteria for PD [19]. The Unified Parkinson's Disease Rating Scale, and diagnostic checklist were completed. *LRRK2* G2019S mutation status was determined as previously described, and 90 of the included individuals were included in a prior report [18]. Family history of Parkinson's disease or parkinsonism in a first degree relative was determined through pedigree assessment completed by physician and/or genetic counselor. In order for a family member to be considered as having parkinsonism, subjects had to have the diagnosis of Parkinson's disease, have been treated with levo-dopa, or have rest tremor plus bradykinesia or postural instability. Because we could not be certain that all exclusionary criteria required for a clinical diagnosis of PD (such as dopamine blocker exposure or stroke) were known in all cases, we refer to risk of parkinsonism rather than risk of PD in the relatives. This study was approved by the Institutional Review Board.

T-tests, Mann-Whitney, and chi-square tests were used for univariate analysis of demographic and disease features, and family history of parkinsonism in the probands. We then evaluated frequency of parkinsonism in parents and siblings of PD subjects, and tested whether parkinsonism risk in the family member varied according to the gender of the proband. As there was only one case of parkinsonism among 335 children, children were not included in the second analysis. Parkinsonism among family members was modeled using a Cox proportional hazards model, first among parents, and second, among siblings, using STATA 8 software (STATA Corp, College Station TX), adjusting the estimates of confidence intervals by using family as a robust variance-covariance estimator (cluster). The

primary outcome was whether gender of the affected proband influenced rates of parkinsonism among their first-degree relatives. Other significant factors associated with family history in the probands or with a putative association with family history were included in the adjusted model, including, age of proband, gender of family member, and whether the proband carried the G2019S mutation.

Results

Complete pedigree information for first-degree relatives was available for 82 women and 93 men with PD. All subjects reported at least one or both parents of Ashkenazic descent except one woman with Sephardic parents. Clinical features of women and men are reported in Table 1. Women and men did not significantly differ in their age at onset or *LRRK2* mutation status. 19 women (23.2%) and 20 men (21.5%) carried the *LRRK2* G2019S mutation. 27 women and 16 men had a first degree family member with parkinsonism, and this represented 17.2% of the overall first degree relatives for men, and 32.9% of the relatives for women (p=0.016). Women were more likely to have a parent with PD than men (28.1%% (23/82) vs. 11.8%% (11/93), p=0.007), but not more likely to have a sibling (6.1% (5/82) vs. 5.4% (5/93)), or children (0% (0/162) vs. 0.58% (1/173)) with parkinsonism.

Thirty-five of the parents of PD probands had parkinsonism, 17 of these were women and 18 were men (Table 2). Age at parkinsonism did not differ between fathers and mothers (mean ages were 80.3 +/− 10.4 years, and 80.7 +/− 8.5 years respectively), and overall average age at death/last contact or age at parkinsonism was also not different (74.1 +/− 14.9 years for the fathers and 76.2 +/− 15.5 years for the mothers). Among parents of PD subjects, having a daughter with PD (p=0.014), older age at time of pedigree (p=0.029) and being part of a *LRRK2* mutation family (p=0.003) were all associated with parkinsonism in the univariate analyses (Table 3). Female gender in the parent was not associated with an increased likelihood of parkinsonism. In the survival model adjusting for *LRRK2* status and accounting for family clustering, the PD subject's age of onset, and parental gender, having a daughter with PD doubled the risk of parkinsonism in the parent (Table 3) (HR=2.19, p=0.023), and having a child with the G2019S mutation almost three-fold increased the risk (HR=2.89, p=0.001). Having a child with early vs. late onset PD did not increase the risk. Among the siblings, having a sister with PD did not increase risk compared with having a brother with PD.

Discussion

Our data support that among individuals of Jewish descent, there is a relatively greater genetic load in women with PD that is not solely accounted for by the G2019S *LRRK2* mutation. While overall penetrance of *LRRK2* mutations is debated, it is known to be incomplete [11,24, 26] and is estimated at between 10 and 70% [13,17,18,30]; it does not appear to depend on gender [22,30]. Thus even though 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 contribute to a different proportion of PD incidence in men versus women. The finding of similar gender distributions among LRRK2 cases [17] is consistent with a recent metaanalysis of the genetic forms of PD, including mutations in SNCA, LRRK2, Parkin and PINK1, whereby approximately 48% of the cases were female [10].

With our study design we cannot determine whether there may still be a gender-specific effect associated with penetrance or expression of *LRRK2* mutations [17]. As we do not have systematic glucocerebrosidase (*GBA*) mutation data, we could not assess whether gender difference in family history may be attributable to mutations in *GBA*, which constitute the

other major genetic determinant of PD in the Ashkenazim and where the sex difference is more similar to that in PD overall [8]. Our study contrasts with others that do not suggest a higher rate of family history in women with PD [1, 7]. This may be related to the ethnic origin of the subjects, although, as noted, the gender difference cannot be attributable solely to *LRRK2* mutations. Because there is the possibility of a type 2 error, we suggest that further study of gender related effects in a larger sample is warranted, including assessment of *GBA* mutations.

The primary limitation of this study is that we performed a family history study based on pedigrees obtained in-person with our patients, but did not examine all relatives using a family study method or verify cases through medical record review [21]. Our rate of family history in a first degree-relative in women with PD was 32.9%, which is higher than most other studies [3,5,7,12,14,23,27,31], although these studies were not done in predominantly Jewish populations. Because some [6], but not all [15], have reported a family information bias where women are more likely to over-report cases of PD, we cannot exclude that some of the observed gender difference may be due to such bias. However, greater reporting bias occurs in recalling sibling's medical states [6], and our finding was robust in the analysis limited to parents. Further, much of the misclassification was in relation to non-PD parkinsonism [6], and our outcome was also parkinsonism and not PD. In order to explain our results, women would have to be twice as likely as men to report a parent with parkinsonism, and the magnitude of the recall bias is unlikely to fully account for the more than two-fold difference between relatives of male and female probands. While many of the parents were deceased and could not be examined, in those few cases for which parents were available for examination, accurate recall did not vary by gender (data not shown). Our results nonetheless warrant further study using more systematic family screen that would limit the potential for family information bias.

Conclusion

The relative genetic contribution may be greater for Jewish women with PD than men with PD, and not just for women with *LRRK2* mutations. Studies evaluating gender differences should include a focus on family history, and larger more systematic studies that include direct family study are needed to determine whether greater genetic loading is present in female probands with PD. Further study that assesses the role of glucocerebrosidase mutations is indicated.

Highlights

1. We compared sex differences in family history in 175 Jewish Parkinson disease (PD) subjects
2. Parents of PD daughters had an increased risk of parkinsonism (HR 2.59, p=0.014)
3. Adjusting for *LRRK2 G2019S* mutations, the increased risk among parents of PD women persisted (HR 2.19, p=0.023)
4. Even accounting for LRRK2 mutations, women with PD have a greater relative genetic load

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Table 1

Clinical features of study subjects

	Men (n=93)	**Women (n=82)**	**p-value**
Age at Exam (Mean±SD)	66.6±12.4	66.7±10.96	0.943
Age at Onset (Mean±SD)	58.98±13.4	59.7±10.6	0.713
***LRRK2* G2019S carrier** (%)	21.5% 20/93	23.2% 19/82	0.792
Report of family history of PD in 1st degree relative(%)	17.2% 16/93	32.9% 27/82	0.016
FH in parent	11.8% (11/93)	28.1% (23/82)	0.007
FH in parent *(among LRRK2 PD)*	25.0% (5/20)	42.1% (8/19)	0.257
FH in parent *(among non-LRRK2 PD)*	8.2% (6/73)	23.8% (15/63)	0.012
FH in siblings	5.4% (5/93)	6.1% (5/82)	0.837

Table 2

Parkinsonism among parents and siblings (total=613 relatives)

Parents of PD Cases				
All Parents n=347	**Parents with parkinsonism n=35 (10.1%)**	**Parents without parkinsonism n=312 (89.9%)**	**Fathers n=173 (49.9%)**	**Mothers n=174 (50.1%)**
Daughter with PD	68.6% (24/35)	44.6% (139/312)	46.8% (81/173) (13/81 with parkinsonism)	47.1% (82/174) (11/82 with parkinsonism)
Son with PD	31.4% (11/35)	55.4% (173/312)	53.2% (92/173) (5/92 with parkinsonism)	52.9% (92/174) (6/92 with parkinsonism)
Child with *LRRK2* Mutation	40.0% (14/35)	19.2% (60/312)	21.4% (37/173) (5/37 fathers of LRRK2 child had parkinsonism)	21.3% (37/174) (9/37 mothers of LRRK2 child had parkinsonism)
Siblings of PD Cases				
Total N=266[a]	**Siblings with parkinsonism** n=12 (4.5%)	**Siblings without parkinsonism** n=254 (95.5%)	**Brothers** n=145 (54.9%)	**Sisters** n=119 (45.1%)
Sister with PD	41.7% (5/12)	44.5% (113/254)	51.7% (61/145) (3/61 with parkinsonism)	47.9% 57/119 (2/57 with parkinsonism)
Brother with PD	58.3% (7/12)	55.5% (141/254)	57.9% (84/145) (4/84 with parkinsonism)	52.1% 62/119 (3/62 with parkinsonism)
Sibling with *LRRK2* Mutation	33.3% (4/12)	23.6% (60/254)	21.3% (31/145) (2/31 with parkinsonism)	27.7% (33/119) (2/33 with parkinsonism)

[a]Gender of 2 siblings unknown, for gender distribution calculations, n=264

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Table 3

Factors associated with Family History of Parkinsonism in First-Degree Relatives

		Univariate Hazards Ratio	**95% CI (p value)**	**Adjusted Hazard Ratio[a]**	**95% CI (p value)**
Parents					
Gender of Child	68.6% daughter with PD 31.4%% son with PD	**2.59**	**1.21–5.54 p=.014**	**2.19**	**1.11–4.30 p=0.023**
Gender of Parent (% woman with parkinsonism)	9.8% mothers with parkinsonism 10.4% fathers with parkinsonism	**0.93**	**.45–1.90 p=.837**	**0.84**	**0.42–1.66 p=0.611**
Age of onset of child with parkinsonism (% with onset <50)	7.5% parents with child with early onset PD had parkinsonism vs. 10.9% parents of child with late onset	**0.51**	**0.19–1.35 p=0.17**	**0.53**	**0.20–1.43 p=0.213**
LRRK2 G2019S mutation in child	18.9% parents from LRRK2 family had parkinsonism vs. 7.7% parents from non mutation family	**3.19**	**1.47–6.93 p=.003**	**2.89**	**1.51–5.52 p=.001**
Siblings[b]					
Gender of Sibling	41.7% sister with PD, 58.4% brother with PD	**0.899**	**0.27–2.92 p=.859**	**0.96**	**0.25–3.66 p=.948**
Gender of sibling (% sisters with parkinsonism)	4.5% sisters w/parkinsonism 4.8% brothers w/parkinsonism	**0.84**	**0.26–2.74 p=.774**	**0.68**	**0.26–2.42 p=.675**
LRRK2 G2019S mutation in sibling	6.25% of siblings from LRRK2 family w/parkinsonism, 3.96% of siblings	**1.62**	**0.47–5.59 p=.447**	**1.22**	**0.27–5.47 p=0.791**

		Univariate Hazards Ratio	95% CI (p value)	Adjusted Hazard Ratio[a]	95% CI (p value)
	from non mutation family				

[a] Adjusted for gender of family member, early onset in proband (<50), LRRK2 family, age at pedigree or age at death (of family member) and included cluster for non-independence among family members;

[b] Sibling model (n=255) as 9 siblings' ages unknown and 2 siblings' genders unknown