LETTER TO THE EDITOR

Sex Distribution of GBA1 Variants Carriers with Dementia with Lewy Bodies and Parkinson's Disease

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A recent article by Ortega et al[1] reported sex-specific differences in *GBA1*-related Parkinson's disease (PD), with an excess of females in carriers of severe variants and of males in carriers of mild variants, although these differences were not confirmed in subsequent reports.[2,3] They hypothesized that this difference might be because of a higher risk of male carriers of *GBA1* severe variants developing dementia with Lewy bodies (DLB) rather than PD. Notable is that we demonstrated sex-specific changes in microglial activation, with male derived being more proinflammatory, and sensitivity to conduritol-b-epoxide inhibition of glucocerebrosidase occurring more often in females.[4]

To investigate the issue of sex specificity in *GBA1*-PD, we further reviewed previously analyzed and reported[5] PD and DLB sequencing data from the publicly available Accelerating Medicines Partnership Parkinson's Disease (AMP-PD; https://www.amp-pd.org, version 2019_v1release_1015). Unlike the other studies, which investigated only the most frequent *GBA1* variants,[1-3] we used Gauchian, a validated tool for comprehensive *GBA1* analysis of Illumina whole-genome sequencing.[5]

A total of 285 PD and 343 DLB cases who carried at least one *GBA1* variant were included, after excluding variants of unknown significance (2 PD, 9 DLB cases). In PD, there was a slight excess of males for severe (19/34; 55.9%), mild (77/131; 58.8%), and risk (67/120, 55.8%) variant carriers (Pearson's χ^2 $P = 0.8829$). In DLB, where a relative excess of males with severe mutations had been hypothesized, the male proportion was 50/79 (63.3%) for severe variant carriers, 46/67 (73.0%) for mild variants carriers, and 143/201 (71.1%) for risk variant carriers (Pearson's χ^2 $P = 0.3566$) (Fig. 1).

Furthermore, the proportion of males with severe variants was similar in PD (55.9%) and DLB (63.3%, Pearson's χ^2 $P = 0.5958$).

Because *GBA1* variants are overall more frequent in DLB than in PD,[5] we wondered whether the higher prevalence of *GBA1* variants in DLB is mainly male driven. Among all *GBA1* PD, 57.2% (163/285) were male. This increased to 69.7% (239/343) in DLB, and the difference was statistically significant (Pearson's χ^2 $P = 0.0016$).

We did not, therefore, observe an excess of males with severe variants in DLB. We also did not replicate the finding of a higher proportion of females among carriers of severe *GBA1* variants with PD. Indeed, adding the numbers of all the individuals with severe *GBA1* variants with PD from our analysis and the previous cohorts,[1-3] there are equal numbers of males and females (76 males and 76 females). This suggests that, despite the overall excess risk of PD in males, the risk posed by severe *GBA1* variants is independent of sex, similar to what was observed for LRRK2 G2019S.[3]

In contrast, we observed a higher proportion of males carrying all classes of *GBA1* variants in DLB than in PD. Because *GBA1* variants are overall more frequent in DLB than in PD,[5] this raises the possibility that the stronger association of *GBA1* variants with DLB is mostly related to males. ■

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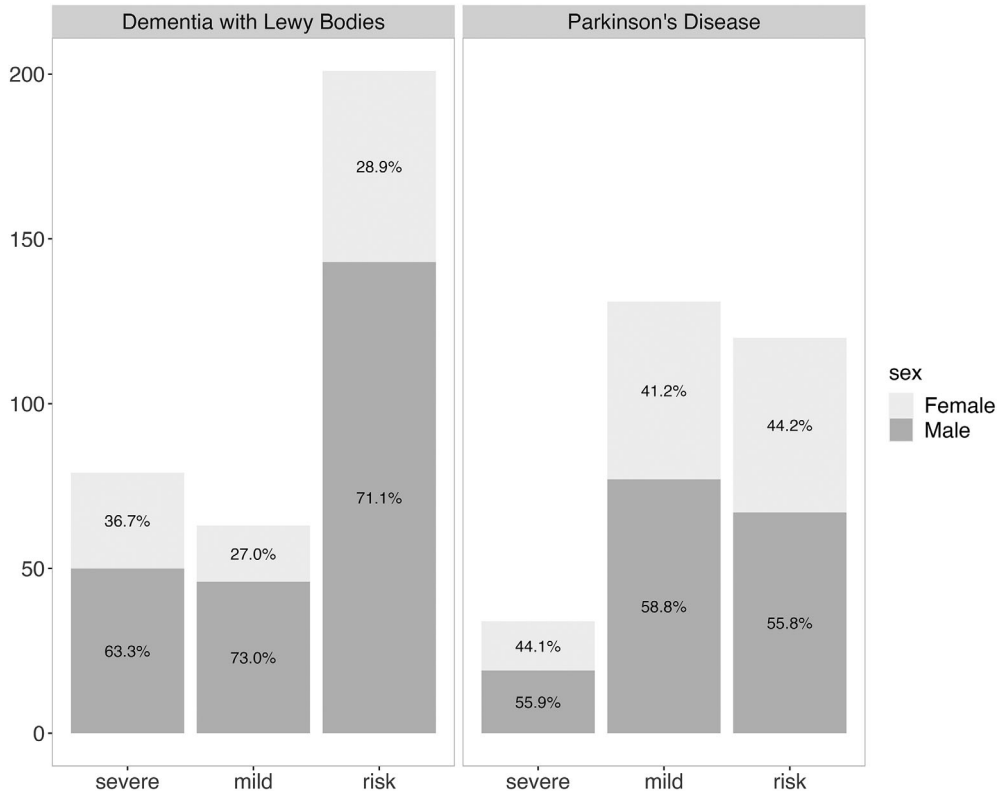

FIG. 1. Number of participants with Parkinson's disease and dementia with Lewy bodies by mutation severity.

information on the study, visit https://www.amp-pd.org. The AMP® PD program is a public-private partnership managed by the Foundation for the National Institutes of Health and funded by the National Institute of Neurological Disorders and Stroke (NINDS) in partnership with the Aligning Science Across Parkinson's (ASAP) initiative; Celgene Corporation, a subsidiary of Bristol-Myers Squibb Company; GlaxoSmithKline plc (GSK); The Michael J. Fox Foundation for Parkinson's Research; Pfizer Inc.; Sanofi US Services Inc.; and Verily Life Sciences. ACCELERATING MEDICINES PARTNERSHIP and AMP are registered service marks of the U.S. Department of Health and Human Services.

Data Availability Statement

The data used to prepare this paper is publicly available at AMP-PD (https://www.amp-pd.org). The code used for the analysis can be found at https://doi.org/10.5281/zenodo.8352764.

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Author Roles

M.T.: study conception, statistical analysis, and writing of the first draft. A.H.V.S.: study conception and manuscript review. C.P.: study conception and manuscript review.

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