LETTER

MIDN locus structural variants and Parkinson's Disease risk

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Dear Editor,

Based on a candidate gene analysis, Obara and colleagues previously reported an association between Parkinson's disease (PD) and deletion structural variants (SV)s at the *MIDN* locus in the Japanese population.[1] In their recent study, using genotyping data from a British cohort, Obara and colleagues further suggest *MIDN* as a confirmed and universal risk factor of PD.[2]

To establish the pathogenicity of *MIDN*, as part of the International Parkinson's Disease Genomics Consortium (IPDGC), we utilized the summary statistics from the most recent PD meta-analysis, which involved 37.7k PD cases, 18.6 U.K. biobank proxy-cases, and 1.4 million controls. Consequently, we did not identify an association with risk of PD at this locus based on common SNP variants (Fig. S1)[3]. In addition, we analyzed whole genome sequencing data (WGS) from eight cohorts totaling 3868 individuals (2742 PD cases and 1126 controls of European ancestry). SVs were genotyped from the WGS using the highly sensitive detection tool Manta.[4] The only major deletion detected was of a reference *Alu* retrotransposon (GRCh38 chr19:1247064-1247368, MAF = 0.014); however, further analysis identified no significant association between the *Alu* deletion and risk for PD ($P = 0.74$, $\beta = -0.03$, SE = 0.22) (Appendix S1). Four additional singleton deletions were detected, including deletions of three reference *Alu* retrotransposons and a 4822-bp deletion that was detected in a healthy control (Fig. S2 and Table S1).

Further, Obara and colleague reported deletions at the *MIDN* locus in 1.64% of controls. In view of this, we utilized gnomadSV, a comprehensive public SV database. This resource provides a call set of ~445k SVs that were detected in 14,891 genomes, spanning four major global populations.[5] In support of our WGS analysis, as shown in (Fig. S3) no common deletion SVs were detected in the general population.

In summary, we did not identify any PD-associated deletions within 100 kb of *MIDN* in the 3,868 individuals analyzed. SV calling using SNP genotyping data is notoriously difficult and it has been repeatedly reported that this method can result in a high false positive rate.[6–8] Due to this factor, SVs require functional validation, which was not presented for the *MIDN* deletions described in the Obara and colleagues' studies. Therefore, the lack of validation of the reported SVs, supported by the lack of evidence of these events in both the gnomadSV data and our WGS analysis, suggests that the *MIDN* deletions reported require further study before they can be unequivocally associated with PD.

Acknowledgments

Conflict of Interest

The authors have nothing to disclose.

References

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Supplementary Methods.
Table S1. Clinical and demographic characteristics of WGS data.
Figure S1. Locuszoom plot of the *MIDN* locus from the most recent PD meta-analysis involving 37.7 PD cases, 18.6 UK biobank proxy-cases and 1.4M controls shows no association with PD based on common variants.
Figure S2. IGV snapshot of a heterozygous 4,822bp deletion (illustrated in red) detected with MANTA in a healthy control individual.
Figure S3. Snapshot of the *MIDN* locus generated by the gnomadSV browser (https://gnomad.broadinstitute.org/region/19-1217850-1294000?dataset=gnomad_sv_r2_1).