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CORRESPONDENCE

ATP10B and the risk for Parkinson's disease

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We read with great interest the article by Martin and colleagues [2] published in *Acta Neuropathologica* in which the authors suggest that compound heterozygous *ATP10B* loss-of-function mutations increase the risk for Parkinson's disease (PD) through lysosomal dysfunction, dysregulated glucosylceramide (GluCer), and phosphatidylcholine (PC) homeostasis. Using exome sequencing and target resequencing, the authors identify 6/617 PD carriers of compound heterozygous *ATP10B* protein-coding, low-frequency variants (minor allele frequency < 0.05) versus 2/597 control carriers of compound heterozygous variants. Segregation analysis of family members was available for some of these individuals. Out of the PD carriers, 4/6 had early onset PD (EOPD, ⩽50 years old). The authors assess the functional impact of a subset of these mutations in cellular assays of lipid translocation, lysosomal function, and cell death. In all but one of the patient-associated mutants tested, impaired ATPase activity, GluCer and PC translocation activity, and lysosomal function were observed, leading to increased cell death.

As part of the International Parkinson's Disease Genomics Consortium's (IPDGC) efforts to examine reported risk and causal factors for PD, we assessed publicly available whole-genome sequencing (WGS) data from the Accelerating Medicines Partnership—Parkinson's disease initiative (AMP-PD) consisting of 1,647 PD patients without known disease-causing mutations (mean AAO 64.2 ± 9.6), of whom 145 cases had EOPD (mean AAO 45.2 ± 4.6), and 1,050 neurologically healthy controls of European ancestry (mean age 60.3 ± 11.9) (www.amp-pd.org). Our WGS analysis identified a total of 43 rare coding variants (MAF < 5%): 42 non-synonymous and one stop-gain, of which six variants were only found in controls and 19 only in PD patients. Despite phase data being unavailable, we identified 1.9% and 2.0% of putative compound heterozygous *ATP10B* carriers in PD and controls, respectively (Fisher's exact test, $p = 0.886$). In the EOPD group, the frequency of putative compound heterozygous carriers was 4.8% (Fisher's exact test, $p = 0.069$ when compared to the control group). Of the nine patient-associated variants tested by Martin et al. p.G671R/p.N865K, shown in vitro to cause significant loss of *ATP10B* ATPase activity and susceptibility to cell death, were present in homozygosity in a control individual aged 52. No PD cases were carriers of homozygous variants. Fisher's exact test did not show significant association of any rare protein-coding variants in PD patients (Table S1, online resource), including the variants described by Martin et al. (Table S2, online resource). Gene-based burden analyses did not detect an enrichment of rare variants in PD cases versus controls (Table S3, online resource).

In a similar manner, we performed a case–control association analysis and burden analyses in imputed genome-wide association study (GWAS) data from 14,671 cases (mean AAO 63.1 ± 12.1) and 17,667 neurologically healthy controls (mean age 61.3 ± 14.4). Of the 842 *ATP10B* variants analyzed (imputation quality Rsq > 0.8), we identified five non-synonymous variants with MAF < 5%, of which three (p.G671R, p.N865K, and p.G393W) were shown by Martin et al. to induce ATP10B loss-of-function in vitro (Table S4, online resource). None of these variants were significantly associated with the disease after Bonferroni correction (threshold for significance = 5.9E-05). We further analyzed data from the largest GWAS meta-analysis versus PD risk (excluding 23andMe data) which comprises 15,056 cases, 18,618 UK Biobank proxy cases (i.e., subjects with a

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first degree relative with PD), and 449,056 controls [3], as well as the most recent age at onset PD GWAS (excluding 23andMe data) consisting of 17,996 cases [1]. No evidence for an association driven by common genetic variation in this gene was found for either PD risk or age at onset (Figure S1, online resource). Finally, gene-based aggregation analysis did not show a consistent cumulative effect of rare variation on PD risk across all the tests applied (Table S3, online resource).

In summary, none of the variants identified as functionally deleterious in vitro that we were able to test have been found to be enriched in PD patients using the largest case–control cohorts publicly available to date. Furthermore, we did not find an enrichment of putative compound heterozygous or homozygous carriers in PD cases (including EOPD) compared to controls, which we would expect to see if *ATP10B* homozygous or compound heterozygous variants were pathogenic, assuming high penetrance. In addition, variants described as deleterious in vitro, and present in 2/6 PD carriers of compound heterozygous mutations described by Martin et al. were present in homozygosity in a control individual. In fact, p.G671R/p.N865K variants are present in homozygosity in 0.03% of individuals in gnomAD (https://gnomad.broadinstitute.org/), arguing against a major role in disease causation. In comparison, the R275W pathogenic *PARK2* variant does not occur as a homozygous variant in any gnomAD individuals. Overall, our findings suggest that there is limited evidence to support *ATP10B* as a disease-causing gene for PD. Large-scale sequencing studies of family trios (particularly EOPD cases) are warranted to firmly establish a role for candidate autosomal recessive PD-causing genes.

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