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CORRESPONDENCE

ATP10B variants in Parkinson's disease: a large cohort study in Chinese mainland population

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Sir,

We have read with great interest the article published recently in *Acta Neuropathologica* by Martin and colleagues [2], in which they reported that the biallelic loss-of-function mutations in the *ATP10B*, encodes a late endo-lysosomal lipid flippase, are associated with Parkinson's disease (PD). The PD-associated *ATP10B* mutants disturbed lysosomal export of glucosylceramide (GluCer) and phosphatidylcholine (PC), and impaired lysosomal functionality and integrity. Moreover, four of six patients with biallelic mutations of *ATP10B* identified in the original study were early onset PD (EOPD; age-at-onset ≤ 50 years old), suggesting that it is worthwhile to further screen for *ATP10B* mutations in EOPD cases. However, follow-up replication studies from different ethnicities debated the pathogenicity of *ATP10B* in PD [4–6].

To investigate the possible role of *ATP10B* in PD, we mined whole-exome sequencing (WES) data from a large familial and case–control cohort of the Parkinson's Disease & Movement Disorders Multicenter Database and Collaborative Network in China (PD-MDCNC, http://pd-mdcnc.com:3111/) [7], consisting of 1,440 sporadic early onset PD patients (sEOPD; age-at-onset ≤ 50 years old), 150 PD families with autosomal recessive (AR) inheritance, and 327 PD families with autosomal dominant (AD) inheritance, as well as 1,357 ethnicity-matched controls (Supplementary Methods, online resource).

While setting the minor allele frequency (MAF) threshold at 5%, 599 low-frequency or rare coding variants (MAF < 5%), including 591 non-synonymous, three non-frameshift deletions, one frameshift deletion, and four stop-gain variants, have been identified in our WES data pooled from unrelated 1,917 probands with PD and 1,357 controls. Specifically, 51 patients (2.66%) have carried homozygous, double-heterozygous, or triple-heterozygous *ATP10B* non-synonymous variants, whereas 28 controls (2.06%) have carried these types of variants of *ATP10B* gene ($p = 0.299$, Table S1, online resource). Among these putative biallelic variant carriers, 40 PD patients and 20 controls carried at least one of three low-frequency variants, rs151210844, rs187173360, and rs184792648, of which the MAF is above 1% in East Asian population. Hence, by setting the MAF filtering threshold at 1% and combining with other facts (detailed descriptions showed in the Supplementary Results), there were only one sEOPD patient carrying the homozygous variant, five sEOPD patients and two controls carrying putative compound heterozygous rare variants

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(MAF < 1%) ($p = 0.484$). To evaluate the pathogenicity of the rare variants, Reve software was applied [7]. One pair of variants (c.1160T>C and c.1091G>T), which were presented in two sEOPD patients and one control, were predicted as damaging variants (Table S2, online resource). Specifically, all three subjects have carried exactly the same two variants (c.1160T>C and c.1091G>T), but one single variant out of these two variants was seldom carried by other subjects. We speculated that this pair of variants were more likely to be a specific haplotype in *cis* location, rather than compound heterozygous variants. In addition, patient EOPD-1274 carried a novel damaging missense variant (c.2503C>T) and a six-base deletion (non-frameshift deletion) present in the nucleotide binding domain of *ATP10B*, which deserved further validation in functional experiments.

To investigate whether variants of *ATP10B* gene confer susceptibility to PD, gene-based burden analysis was conducted by SKAT-O; however, no excess burden of rare or low-frequency variants of *ATP10B* gene was detected in our cohort (Table S3, online resource), which is consistent with the results of European-ancestry subjects [3]. Then, we thoroughly examined the associations between the common or low-frequency variants (MAF ≥ 1%) of *ATP10B* and the risk of PD. 17 common or low-frequency variants had been identified in our cohort (Supplementary Methods, online resource), but none showed significant difference between PD patients and controls either in the additive model or in the recessive model (Table S4, online resource).

With the exception of p.I1222T, the variants found as compound heterozygous in PD patients from the original article had not been identified in our cohort. Taken together, the burden analysis did not establish an association between all rare variants or rare recessive variants of *ATP10B* and PD in our large familial and case–control cohort. Besides, no evidence of an association driven by common or low-frequency genetic variation in *ATP10B* was found for PD risk in the Chinese population, similar to the result of the recently published study in replication cohort from European ancestry [1, 3, 6]. The major limitation about our study is the putative compound heterozygous variants were not assessed completely, since there is no information on the phase, although we have verified the rare variants. In conclusion, our data could not rule out the potential role of *ATP10B* biallelic variants in PD, but *ATP10B* may not play a major role in PD patients. Additional large-scale familial and case–control studies in different ethnic backgrounds are necessary to determine whether *ATP10B* is associated with PD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00401-021-02280-9.

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