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Letter to the Editor

In reply to the letter to the editor regarding "TGM6 variants in Parkinson's disease: clinical findings and functional evidence"

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Dear Editor:

We appreciate the letter to the editor (Hall et al., 2020) concerning (Chen et al., 2020a). Our study detected low-frequency *TGM6* variants in patients with Parkinson's disease (PD) and provided experimental results indicating the role of *TGM6* variants in PD pathogenesis. Hall et al. (2020) conducted whole-genome sequencing (WGS) analysis using data from the "*Accelerating Medicines Partnership - Parkinson's Disease*" (AMP-PD) initiative. None of the *TGM6* variants in our study were observed. The results of association analyses did not support the relationship between *TGM6* variants and PD in the population. Their points are important, and we are grateful to have the opportunity for further discussion.

We think that inter-ethnic differences exist in genetic variants. The presence of high-risk variants can differ substantially by ethnicity. For example, the contribution of *GBA* variants to PD is racial dependent. *GBA* p.R496H and 84insGG were reported to increase PD risks exclusively in Ashkenazi Jewish (AJ) populations (Zhang et al., 2018). Regarding *TGM6* variants, as shown in Table 1 in Hall et al. (2020), the frequency of *TGM6* variants varies considerably between Europeans and East Asians, according to data from gnomAD. However, most patients in AMP-PD are Europeans, accounting for 93.8% (https://amp-pd.org). The results can be different in Asians. Second, *TGM6* p.P359L was previously reported in a PD pedigree from Serbia (Westenberger et al., 2016) and further investigated in our experiments. This variant was not found in our participants or AMP-PD patients, indicating the diversity in PD genetics among different populations. Third, it confuses us that the *TGM6* variants described in our research present with frequency in gnomAD, but all of them were not detected in AMP-PD in Table 1 in Hall et al. (2020). Perhaps the percentages of different races in the two databases have some influence? The proportions of Asian, Latino and African are much more significant in gnomAD than that in AMP-PD.

Based on ethnic differences, the association analysis results of Hall et al. (2020) cannot be applied to Han Chinese. We plan to perform WGS in asymptomatic controls to analyze the effect of *TGM6* variants and other Han Chinese risk factors to determine whether missense mutations in the *TGM6* will exclusively increase PD risks.

It is worth noting that the genetic findings of *TGM6* are not consistent across recent studies. On the one hand, *TGM6* p.R111C and *TGM6* p.L517W have been reported to be pathogenic and associated with spinocerebellar ataxia type 35 (SCA35). But these two variants appeared in PD patients in our research. Compared with the wild type, their overexpression was related to higher α-synuclein levels and lower autophagy efficiency. On the other hand, Chen et al. (2020b) reported the non-segregation of *TGM6* p.L517W with phenotype in a pedigree with ataxia and questioned the pathogenicity of *TGM6* in SCA35. It highlights the necessity of assessing variant pathogenicity through sequencing from phenotypically different patients. More research on *TGM6* in cellular and biological processes can help determine the complex functional relationships between these variants and different diseases.

Abbreviations

AJ, Ashkenazi Jewish; PD, Parkinson's disease; SCA35, spinocerebellar ataxia type 35; WGS, whole-genome sequencing.

Author contributions

K.C. and YX. Z. analyzed the data and reviewed the literature; K. C. and Y.T. wrote the paper.

Ethics approval and consent to participate

All authors hereby declare that this study involving human participants has been approved by the ethics committee of Huashan Hospital. Informed consent was obtained from all individual participants included in the study.

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Conflict of Interest

The authors declare no conflict of interest.

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