Letter to the Editor

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

Kui Chen1,2, Yan Tan1 and Yan-Xin Zhao1,*

1Department of Neurology, Shanghai Tenth People’s Hospital, Tongji University, School of Medicine, 301 Middle Yanchang Road, 200072, Shanghai, P. R. China
2Department of Neurology & National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University, 12 Wulumuqi Zhong Road, 200040, Shanghai, P. R. China
*Correspondence: zhao_yanxin@126.com (Yan-Xin Zhao)

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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 Y.X. 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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