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Letter to the Editor

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

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Dear Editor:

We read with interest the recent article by Chen et al. (2020) published in the *Journal of Integrative Neuroscience* in which the authors suggest that three rare variants in *TGM6*, encoding transglutaminase 6 (TG6), are associated with Parkinson's Disease (PD). This is notable because the *TGM6* locus was not associated with PD in the most recent meta-analysis of PD GWAS (Nalls et al., 2019). The authors used targeted gene sequencing to identify eleven rare variants of *TGM6* in idiopathic PD patients, including two previously known function-altering rare variants of *TGM6*, p.R111C and p.L517W. The authors demonstrated that overexpression of these three *TGM6* mutants correlated with reduced TG6 activity, increased levels of α-synuclein, and decreased autophagy flux compared to the wild-type, suggesting a link between *TGM6* variants and PD pathogenesis.

As part of the International Parkinson's Disease Genomics Consortium's (IPDGC) efforts to examine reported genetic risk factors for PD, we assessed genetic variation in *TGM6* using 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 age at onset (AAO) 64.2 $\pm$ 9.6), of which 145 cases had early-onset PD (mean AAO 45.2 $\pm$ 4.6), and 1,050 neurologically healthy controls of European ancestry (mean age 60.3 $\pm$ 11.9)[1]. Our WGS analysis identified 15 rare coding variants (MAF $<$ 5%): 12 nonsynonymous, of which 1 variant was only found in controls (Table 1). None of the variants described by Chen et al. (2020) were detected in our analysis.

Association analyses of *TGM6* variants and PD risk were then performed using RVTESTS package v.2.1.0 (Zhan et al., 2016). Case-control association testing using a single-variant score test adjusted by covariates (including sex, age, and 10 principal components) identified no significant differences in TGM6 variants' frequency between PD cases and controls after Bonferroni correction (significance threshold = 0.05/362 = 1.38E-04). Gene-based burden analyses, again using RVTESTS v.2.1.0, did not detect an enrichment of rare *TGM6* variants in PD cases versus controls (SKAT-O with MAF $<$ 0.03 *P*-values were 0.7733 for all variants and 0.6890 for coding variants). All code used can be found here: (https://github.com/ipdgc/IPDGC-Trainees/blob/master/TGM6_RARE_VARIANT_ANALYSIS.md).

In conclusion, our analyses presented here do not support a role for *TGM6* variants as a risk factor for PD in our cohort. We did not find any *TGM6* variants enriched in PD versus controls, and the additive effects of multiple *TGM6* variants were not found to represent a significant burden for PD. Notably, none of the variants identified by Chen et al. (2020) were observed in our dataset. However, the vast majority of our data is of European ancestry, while Chen et al. (2020) carried out their work in a Chinese population. PD is genetically complex and heterogeneous, and different genetic contexts may influence the importance of variants in the disease. Therefore, our analysis cannot rule out a role for rare *TGM6* variants in non-European populations and highlights the need for further study in diverse ancestries.

Author contributions

Writing and original draft preparation by AH. Methodology, formal analysis and data interpretation by KJB. Review and editing by JPQ. Datasets provided by the IPDGC. All authors have read and agreed to the published version of the manuscript.

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[1] The Accelerating Medicine Partnership in Parkinson's Disease (AMP-PD). (2020) Available at: https://amp-pd.org/

Table 1. Frequency of rare coding variants detected in AMP-PD WGS data (grey).

		gnomAD		AMP-PD				
Variant	**rsID**	**Frequency (European non-Finnish)**	**Frequency (East Asian)**	**Frequency (cases)**	**Frequency (controls)**	**OR**	**CI 95**	***P*-value (single-variant test)**
p.W11G	rs141178275	0.00003149	0	0.001518	0.001429	1.063	0.2537-4.451	0.64927
p.S14S	rs149394698	0.005994	0.00005017	0.006982	0.01095	0.635	0.3553-1.135	0.827472
p.S39C	rs144201778	0.0007248	0	0.0006072	0.0009524	0.6373	0.0897-4.528	0.18099
p.M93V	rs146529216	0.00005423	0	0.003643	0.001429	2.556	0.7204-9.067	0.0433451
p.A141E	rs73894929	0.0006889	0	0.0003036	0.0009524	0.3186	0.02887-3.515	0.369187
p.S159S	rs16984872	0.008834	0	0.009715	0.0119	0.8142	0.4812-1.378	0.843633
p.G243S	rs202245813	0.00003542	0	0.0009107	0.001905	0.4777	0.1068-2.136	0.712623
p.N331S	rs138323389	0.00002325	0	0	0.001429	0	0	0.907626
p.E337E	rs142832802	0.0007279	0	0.001214	0.0004762	2.552	0.285-22.85	0.409379
p.E406K	rs144338465	0.002036	0.00005013	0.001821	0.0009524	1.914	0.386-9.493	0.967385
p.R448W	rs147979536	0.01958	0.001255	0.01913	0.01381	1.392	0.8939-2.169	0.227511
p.G508D	rs140719871	0.002588	0	0.002429	0.001905	1.276	0.3837-4.242	0.659792
p.V527E	rs61729226	0.0004252	0	0.0009107	0.0009524	0.9562	0.1596-5.728	0.508315
p.P564S	rs200674917	0.0005886	0	0.0006072	0.0004762	1.275	0.1156-14.07	0.923033
p.R665S	rs138807504	0.001883	0.0001504	0.003947	0.004762	0.8281	0.3625-1.892	0.693725
p.R111C	rs372250159	0.00000774	0.0002005	-	-	-	-	-
p.L517W	rs387907097	0	0.002011	-	-	-	-	-
p.V208M	rs61743614	0.00003098	0	-	-	-	-	-
p.V255M	rs751618387	0.00003878	0	-	-	-	-	-
p.G199S	rs182249285	0.00004396	0.0004893	-	-	-	-	-
p.V314M	rs202184911	0.000007744	0.005362	-	-	-	-	-
p.P347L	rs183670042	0	0.006716	-	-	-	-	-
p.A34G	rs566673079	0	0	-	-	-	-	-
p.R81W	NA	NA	NA	-	-	-	-	-
p.R540G	rs61740142	NA	0.0006383	-	-	-	-	-
p.V391M	rs116904482	0.0001006	0.009422	-	-	-	-	-

Odds ratio (OR), 95% confidence interval (CI 95) and *P*-value of single-variant score test are presented. For comparison, frequencies in the gnomAD database for European non-Finnish and East Asian cohorts are included. The gnomAD frequencies in the same cohorts for the variants described by Chen et al. (2020), and not detected in our analysis of AMP-PD, are also presented (bottom).

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Conflict of Interest

The authors declare that they have no conflict of interest.

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