Is SH3GL2 p.G276V the Causal Functional Variant Underlying Parkinson's Disease Risk at this Locus?

We read with great interest the article by Bademosi and colleagues,[1] where they investigated the role of *SH3GL2* p.G276V on neuron dysfunction in Parkinson's disease (PD).

The *SH3GL2* gene encodes the endophilin-A1 (EndoA1) protein, crucial for synaptic vesicle endocytosis and blood–brain barrier permeability regulation.[1] Two *SH3GL2* independent signals have been identified to potentially increase PD risk in the latest European genome-wide association studies (GWAS) meta-analysis: rs13294100 and rs10756907.[2]

Exome sequencing on a German cohort suggested the p.G276V variant as an independent PD risk factor. Bademosi et al[1] recently demonstrated that p.G276V impairs Ca2+ influx-induced synaptic autophagy without destabilizing EndoA1. The authors found that the human p.G276V protein was stable but showed a significant decrease in the number of autophagosomes compared with control neurons.

To clarify the association between *SH3GL2* and PD, we leveraged whole-genome sequencing (WGS) data from the Accelerating Medicines Partnership-Parkinson's Disease (AMP-PD; https://amp-pd.org/) release 3.0, consisting of 3,105 cases and 3,670 controls from European descent, and large-scale genotyping imputed data from the Global Parkinson's Genetics Program (GP2; https://gp2.org/) release 5.0, consisting of 12,728 cases and 10,533 controls from 10 different ancestries. Quality control analyses are described elsewhere (https://github.com/vitale199/GenoTools/). Variants were annotated using ANNOVAR, and Fisher's exact test was applied using PLINK 1.9. Summary statistics from the latest PD risk GWAS meta-analyses were assessed.[2-5] We leveraged data from the omicSynth data resource looking at quantitative trait loci (QTL). Gene-based burden analyses were performed by using RVTESTS.

We identified 14,590 *SH3GL2* variants in AMP-PD (Supplementary Table S1). Likewise, 30,719 variants were identified in GP2 (Supplementary Table S1). The p.G276V variant was found in Europeans in both AMP-PD (one case, two controls) and GP2 (three cases, one control); however, no association was found with PD risk (AMP-PD: $P = 0.394$, odds ratio [OR] = 1.296; GP2: $P = 0.869$, OR = 1.034) (Table 1). This variant was also identified in GP2 in three African American (AAC) controls and one Ashkenazi Jew (AJ) PD patient.

No linkage disequilibrium (LD) was observed between p.G276V and the European GWAS lead single nucleotide polymorphisms (SNPs). Conditional analyses suggested that these variants were most likely independent signals. No significant association between *SH3GL2* common genetic variation and PD risk was identified in the Latino nor Asian populations.[4,5] The analysis of a multi-ancestry population[3] identified the intronic variant rs910316833 as the most significant SNP (Supplementary Fig. S1).

The QTL analysis revealed six potential functional impacts for *SH3GL2* (top SNPs: rs2145659, rs3758217, rs10756899, and rs2383044). Finally, no cumulative effect of multiple genetic variants within *SH3GL2* on PD risk was found after conducting rare variant burden meta-analyses.

Using the largest case–control genetic cohorts publicly available to date in the PD field, the p.G276V variant was found in both AMP-PD and GP2 in Europeans; however, this variant was not associated with PD risk and consequently does not causally explain the PD GWAS significant association at the *SH3GL2* locus.

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TABLE 1 SH3GL2 *p.Gly276Val variant identified in the AMP-PD and GP2 datasets*

Location[a]	Variant	A1	A2	Cohort	F (Cases)	F (Controls)	OR (95% CI)	*P*-value
9: 17793465	p.Gly276Val rs150543523	T	G	AMP PD	0.003275	0.002528	1.296	0.3944
				GP2 AAC	0	0.001455	NA	0.3589
				GP2 AFR	0	0	NA	NA
				GP2 AJ	0.000676	0	NA	0.4701
				GP2 AMR	0	0	NA	NA
				GP2 CAS	0	0	NA	NA
				GP2 EUR	0.003955	0.003828	1.034 (0.69780–1.531)	0.8693
				GP2 SAS	0	0	NA	NA
				GP2 MDE	0	0	NA	NA
				GP2 FIN	0	0	NA	NA

[a]Chromosomal location is given according to GRCh38/hg38.
Abbreviations: A1, effect allele; A2, reference allele; AAC, African American; AFR, African; AJ, Ashkenazi Jew; AMP-PD, Accelerating Medicines Partnership–Parkinson Disease; AMR, Admixed American/Latin American; CAS, Central Asian; EUR, European; F, allele frequency (A1); FIN, Finnish; GP2, Global Parkinson's Genetics Program; MDE, Middle Eastern; NA, not applicable; OR (95% CI), odds ratio with 95% confidence intervals; SAS, South Asian.

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Data Availability Statement

All GP2 data is hosted in collaboration with the AMP PD, and is available via application on the website (https://amp-pd.org/register-for-amp-pd; https://doi.org/10.5281/zenodo.7904832). Genotyping imputation, quality control, ancestry prediction, and processing was performed using GenoTools v1.0, publicly available on GitHub (https://github.com/GP2code/GenoTools). All scripts for analyses are publicly available on GitHub (https://github.com/GP2-TNC-WG/GP2_TRAINEES-SH3GL2/; Zenodo DOI: https://doi.org/10.5281/zenodo.10257319).

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Computerized Cognitive Training Increases Gray Matter Volumes in Huntington's Disease: A Pilot Study

Computerized cognitive training (CCT) aims to improve cognition through practice on tasks that invoke targeted cognitive domains. CCT improvements to cognition and gray matter structure have been found in healthy older adults and clinical populations.[1,2] However, its effects in Huntington's disease (HD) have not been thoroughly examined.[3]

We conducted a pilot randomized controlled trial to examine the effects of CCT in pre-manifest and early-stage HD. Participants were randomized to either multidomain CCT (two 1-hour sessions weekly) or lifestyle education (monthly newsletters) over 3 months. A sub-sample of participants (n = 6 CCT, n = 10 lifestyle education) completed structural magnetic resonance imaging and cognitive assessments at baseline and follow up. We predicted increased or preserved gray matter volumes in

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