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Replication assessment of *NUS1* variants in Parkinson's disease

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Abstract

The *NUS1* gene was recently associated with Parkinson's disease (PD) in the Chinese population. Here, as part of the International Parkinson's Disease Genomics Consortium, we have leveraged large-scale PD case-control cohorts to comprehensively assess damaging *NUS1* variants in individuals of European descent. Burden analysis of rare nonsynonymous damaging variants across case-control individuals from whole-exome and -genome data sets did not find evidence of *NUS1* association with PD. Overall, single-variant tests for rare (minor allele frequency<0.01) and common (minor allele frequency>0.01) variants, including 15 PD-GWAS cohorts and summary statistics from the largest PD GWAS meta-analysis to date, also did not uncover any associations.

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CRediT authorship contribution statement

Bernabe I. Bustos: Conceptualization, Methodology, Formal analysis, Resources, Writing - original draft, Writing - review & editing. **Sara Bandres-Ciga:** Resources, Writing - review & editing. **J. Raphael Gibbs:** Resources, Formal analysis. Writing - review & editing. **Dimitri Krainc:** Funding acquisition, Writing - review & editing. **Niccolo E. Mencacci:** Conceptualization, Writing - review & editing. **Ziv Gan-Or:** Conceptualization, Writing - review & editing. **Steven J. Lubbe:** Conceptualization, Supervision, Writing - original draft, Writing - review & editing.

Disclosure

D.K. is the Founder and Scientific Advisory Board Chair of Lysosomal Therapeutics Inc. D.K. serves on the scientific advisory boards of The Silverstein Foundation, Intellia Therapeutics, and Prevail Therapeutics and is a Venture Partner at OrbiMed. B.I.B, S.B-C, J.R.G, N.E.M, Z.G-O and S.J.L. declare that they do not have conflict of interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.10l6/j.neurobiolaging.2020.11.007.

Our results indicate a lack of evidence for a role of rare damaging nonsynonymous *NUS1* variants in PD in unrelated case-control cohorts of European descent, suggesting that the previously observed association could be driven by extremely rare population-specific variants.

Keywords

NUS1; Rare-variant burden; Parkinson's disease

1. Introduction

The *NUS1* gene encodes an endoplasmic dehydrodolichyl diphosphate synthase subunit that promotes trafficking of low-density lipoprotein–derived cholesterol (Harrison et al., 2009, 2011). A significant burden of rare (minor allele frequency [MAF]<0.01) damaging nonsynonymous *NUS1* variants was recently identified in 2 large independent Chinese case-control cohorts (Guo et al., 2018). Replication in a smaller Chinese cohort found no association with Parkinson's disease (PD) (Chen et al., 2020). Here, as part of the International Parkinson's Disease Genomics Consortium (IPDGC), we assessed a compendium of large-scale PD case-control cohorts to investigate damaging *NUS1* variants in PD populations of European descent.

2. Results

Using the IPDGC whole-exome sequencing (WES) data (Jansen et al., 2017) and the Accelerating Medicines Partnership–Parkinson's disease initiative (AMP-PD) whole-genome sequencing (WGS) data (https://amp-pd.org/whole-genome-data), we only identified 2 heterozygous rare (MAF<0.01), damaging (CADD>12.37) nonsynonymous *NUS1* variants: p.P169 R and p.K214 E (Table 1). None of the originally reported 18 variants were observed. We identified single heterozygous carriers of p.P169 R and p.K214 E in PD cases and none in controls in the IPDGC-WES data (1/1040 cases vs. 0/452 controls). In the AMP-PD WGS data, we observed 5 PD cases and 5 controls harboring p.P169 R (5/1647 cases vs. 5/1050 controls) and one case and control carrying p.K214 E (1/1647 vs. 1/1050 controls). Assuming a global disease prevalence of 0.5% and the originally reported carriership frequency of 0.003 (28/9512), we have a 100% power to detect an odds ratio of 11.5 at $p = 0.049$, for both IPDGC WES and AMP-PD cohorts. No significant burden differences were observed between cases and controls (Table 1). Additional burden tests (gene- and allele-based) failed to uncover any significant enrichment (see Supplementary Information).

We next explored single-variant associations, using rare and common variants separately, within *NUS1* plus 10kb flanking regions. None of the 6 and 328 rare variants observed in the IPDGC-WES and AMP-PD WGS data, respectively, showed significant association (See Supplementary Information). Two rare intronic variants in the IPDGC-GWAS cohorts (total number of variants observed is 36) survived multiple testing correction: rs144827068 (p=1.6×10^{-3}) and rs187218668 (p=1.7×10^{-3}) (Supplementary Table 1). Although suggestive associations with common variants were observed in the AMP-PD WGS cohort (rs74498762: p=1.07×10^{-3}, OR=0.40, SE=0.28; rs143797072: p=1.51×10^{-3},

OR=0.63, SE=0.15; Supplementary Table 2 and Supplementary Fig. 1, upper panel), assessment of *NUS1* common variants in the IPDGC-GWAS data and summary statistics from the most recent PD GWAS meta-analysis (Nalls et al., 2019) failed to uncover conclusive associations (Supplementary Fig. 1, middle and lower panel).

3. Conclusions

Here, we performed a comprehensive assessment of *NUS1* variants using the largest available PD genetic data sets of European descent. We did not observe any evidence of enrichment of rare damaging nonsynonymous variants in PD cases compared with controls. At the single-variant level, although we observed some suggestive associations, the largest meta-analysis of PD GWAS data (Nalls et al., 2019) did not uncover any associated *NUS1* variants. The lack of evidence here supports the previous failure to replicate in Chinese population (Chen et al., 2020); however, we note that it was somewhat statistically underpowered because of the small sample size, a similar limitation we faced in our rare single-variant tests. Although we cannot exclude a possible role for rare *NUS1* variants in the European population, the fact that most of the original variants are extremely rare and mostly present in Asian populations (Supplementary Table 3) suggests that they are likely population specific. Additional large-scale familial and case-control studies in non-European ancestry populations are needed to further evaluate the role of *NUS1* in PD etiology.

4. Methods

We used 4 large sets of available PD case-control cohorts of European ancestry (See Supplementary Information). Variant annotation and selection are described in the Supplementary Information. For rare nonsynonymous variant burden tests, we leveraged carriership counts in cases and controls using Fisher's exact test. For single rare variant tests (MAF<0.01), we assessed allelic, genotypic, trend, dominant, and recessive models with Fisher's exact test. For single common variant tests (MAF>0.01), we used a logistic regression. Multiple testing was accounted for by Bonferroni correction. More detailed descriptions are available in the Supplementary Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Burden analysis of rare damaging nonsynonymous variants within the *NUS1* gene in the IPDGC-WES and AMP-PD WGS data sets

CHR	BP	REF	ALT	LOC	Exon	Type	Variant	CADD	dbSNP	gnomAD Eur	IPDGC-WES			AMP-PD WCS			Combined		
											Cases	Controls	*P*-value	Cases	Controls	*P*-value	Cases	Controls	*P*-value
6	118,014,295	C	G	exonic	2	nsn	p.P169R	19.26	rs150646335	0.002	1	0	1.00	5	5	0.56	6	5	0.58
6	118,015,292	A	G	exonic	3	nsn	p.K214E	18.02	rs146171115	0.0006	1	0		1	1		2	1	

Key: ALT, alternative allele; AMP-PD, Accelerating Medicines Partnership–Parkinson's disease initiative (https://amp-pd.org/); BP, base pair; CADD, Combined Annotation Dependent Depletion (https://cadd.gs.washington.edu/); CHR, chromosome; dbSNP, The Single Nucleotide Polymorphism Database (https://www.ncbi.nlm.nih.gov/snp/); Exon, exon number; Freq, frequency; gnomaAD Eur, European (non-Finnish) frequency from the Genome aggregation consortium (https://gnomad.broadinstitute.org/); IPDG, International Parkinson's Disease Genomics Consortium (https://pdgenetics.org/); LOC, variant location; nsn, nonsynonymous; REF, reference allele; WES, whole-exome sequencing; WGS, whole-genome sequencing.

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