UK Biobank subjects carrying protein truncating variants in *HERC1* are not at substantially increased risk of minor psychiatric disorders

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Short title: ***HERC1* protein truncating variants**

Funding

No external funding

In a recent study of carriers of protein truncating variants (PTVs) in genes implicated in schizophrenia by the SCHEMA exome sequencing study, we reported that carriers among UK Biobank participants appeared to be generally healthy without showing subclinical features of psychiatric illness or impairment of functioning (Curtis, 2022; Singh and The Schizophrenia Exome Meta-Analysis (SCHEMA) Consortium, 2022). However we did note the possible exception that there were somewhat increased rates of affective disorders among carriers of PTVs in *HERC1*. The strongest indication of this was that among *HERC1* PTV carriers, 32 had answered No to the question as to whether they had seen a doctor (GP) for nerves, anxiety, tension or depression whereas 37 had answered Yes. In the whole sample the proportions for these answers where 0.65 and 0.34. Taken in isolation, this result would have been significant at 0.0008 but because multiple genes and phenotypes were considered it was not possible to draw any formal conclusion. Instead, these results could be considered as hypothesis-generating, suggesting that carriers of PTV variants in *HERC1* might in general be at higher risk of minor mental disorders such as would result in consultation with a GP.

In order to test this, a case-control study was performed in the newly released cohort of 270,000 exome-sequenced UK Biobank participants. UK Biobank had obtained ethics approval from the North West Multi-centre Research Ethics Committee which covers the UK (approval number: 11/NW/0382) and had obtained written informed consent from all participants. The UK Biobank approved an application for use of the data (ID 51119) and ethics approval for the analyses was obtained from the UCL Research Ethics Committee (11527/001). The UK Biobank Research Analysis Platform was used to access the Final Release Population level exome OQFE variants in PLINK format for 469,818 exomes which had been produced at the Regeneron Genetics Center using the protocols described here: https://dnanexus.gitbook.io/uk-biobank-rap/science-corner/whole-exome-sequencing-oqfe-protocol/protocol-for-processing-ukb-whole-exome-sequencing-data-sets (Backman et al., 2021). All variants were then annotated using the variant effect predictor software (McLaren et al., 2016) and this information was used to identify participants who carried a PTV in *HERC1*, consisting of a stop, splice site or frame shift variant. Attention was restricted to participants who had not been among the 200,000 analysed in the previous study and who had a Yes or No answer for "Seen doctor (GP) for nerves, anxiety, tension or depression" (data item 2090-0.0).

Of participants who were not *HERC1* PTV carriers, 307196 (66.0%) answered No and 158191 (34.0%) answered Yes, while among the PTV carriers 87 (64.4%) answered No and 48 (35.6%) answered Yes, chi-squared = 0.147, 1 df, p = 0.70.

In contrast to the original findings, in the new sample the proportion of participants answering positively is nearly the same between carriers and non-carriers of *HERC1* PTVs. It is not the case that *HERC1* PTVs generally result in poorer psychological functioning such that carriers have a markedly increased risk of minor psychiatric disorders.

Acknowledgments

This research has been conducted using the UK Biobank Resource under Application Number 51119.

This work was carried out in part using resources provided by BBSRC equipment grant BB/R01356X/1. The author wishes to acknowledge the staff supporting the High Performance Computing Cluster, Computer Science Department, University College London. The author wishes to thank the participants who volunteered for the UK Biobank project.

Conflicts of interest

The author denies any conflict of interest.

Availability of data

The raw data is available on application to UK Biobank. Detailed results are not provided in order to protect confidentiality. Code and scripts use to extract the data and perform the analyses are available at *https://github.com/davenomiddlenamecurtis*.

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