Haploinsufficiency of the *HIRA* gene may not always produce severe neurodevelopmental consequences

David Curtis *d.curtis@ucl.ac.uk*

ORCID 0000-0002-4089-9183

Abstract

A recent report describes neurodevelopmental disorder in a total of three unrelated patients with *de novo* truncating variants in the *HIRA* gene. 200,632 subjects who have undergone exome sequencing by the UK Biobank were investigated to identify any with variants predicted to cause *HIRA* haploinsufficiency. Four were found, three with frameshift variants and one with a stop variant. One of these subjects had depression but the others did not have any major neuropsychiatric phenotypes. Variants causing haploinsufficiency of HIRA are very rare but when they do occur it seems that they are not always associated with neurodevelopmental disorder.

This research has been conducted using the UK Biobank Resource.

Keywords

HIRA; 22q11DS; UK Biobank; exome.

Acknowledgments

This research has been conducted using the UK Biobank Resource. 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.

Introduction

A recent report describes neurodevelopmental disorder in a total of three unrelated patients with *de novo* truncating variants in the *HIRA* (Histone cell cycle regulation defective, S. Cerevisiae, homolog of, A) gene, which is situated within the critical region of the 22q11.2 deletion syndrome (Jeanne et al., 2021). They also found a subject with a *de novo* missense variant of unknown significance who had been included in an autism spectrum disorder cohort. *Hira* knockdown in mice was associated with impaired dendritic growth and branching and neuroanatomical defects. The authors proposed that *HIRA* haploinsufficiency might contribute to the neurodevelopmental phenotype observed in 22q11DS.

The UK Biobank consists of a sample of 500,000 volunteers. Of these, sequence data is available for 200,632 subjects who have undergone exome-sequencing, quality control and genotyping by the UK Biobank Exome Sequencing Consortium using the GRCh38 assembly with coverage 20X at 95.6% of sites on average (Szustakowski et al., 2020). We investigated this sample to see whether any subjects had variants predicted to cause haploinsufficiency of *HIRA* in order to assess whether this was associated with neuropsychiatric phenotypes.

Methods

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 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). All variants were annotated using the standard software packages VEP, PolyPhen and SIFT (Adzhubei et al., 2013; Kumar et al., 2009; McLaren et al., 2016). GENEVARASSOC and SCOREASSOC were used to identify subjects with variants predicted to cause haploinsufficiency, consisting of stop, frameshift and essential splice site variants, and for these subjects R was used to extract fields containing clinical information regarding diagnosis, treatment and responses to questions about mental health (Curtis, 2012; R Core Team, 2014). Different items are completed by different subjects and attention was focussed on those fields which were most frequently completed, including fields relating to depression and anxiety, fluid intelligence, reported diagnoses, prescribed medication, educational attainment and employment status. In order to check genotype call quality, for the subjects bearing these variants the CRAM files detailing individual reads were downloaded from UK Biobank and visualised in version 2.9.4 of the Integrative Genomics Viewer (IGV) (Robinson et al., 2017).

Results

Four subjects were identified with the following variants, each predicted to cause haploinsufficiency: chr22:19353473GC>G; chr22:19388543CAG>C; chr22:19356982GA>G; chr22:19351429G>A. The first three of these are frameshift mutations and the fourth is a stop variant. Ensembl lists two protein coding transcripts for *HIRA*, ENST00000263208.5 (corresponding to RefSeq mRNA NM_003325.4) and ENST00000340170.8. Three of the variants impact both transcripts whereas chr22:19356982GA>G is intronic for ENST00000340170.8. Table 1 presents this information alongside a summary of the phenotypic information obtained from these subjects. In order to guard participant confidentiality detailed responses are not presented. Subject C reported depression, having seen a GP and a psychiatrist and was prescribed an antidepressant. Subject B had responded positively to a few touch screen items such as “Miserableness” but denied frequent depression and did not report any mental health diagnosis or treatment. Subject A and D denied mental health problems. Subjects A, B and C did not have impaired intelligence or educational attainment and were employed at time of assessment. Subject D left school at 15 with no qualifications and reported being unable to work because of disability, although they did report having back problems and other physical health problems which could account for this. Reads covering all four variants were visualised in IGV and the calls appeared to be of good quality. Read depths ranged from 36 to 76 with no marked allele balance bias and with the variant being observed in reads from both positive and negative strands. Snapshots for these reads are presented in Supplementary Figure 1.

Discussion

It is clear that the four subjects predicted to have *HIRA* haploinsufficiency do not have severe neuropsychiatric problems. One of the variants, carried by subject C, only impacts one of the transcripts but in fact C is the only subject who clearly has a psychiatric diagnosis. We should bear in mind that UK Biobank participants are self-selected so that if *HIRA* haploinsufficiency only caused problems for a proportion of subjects then UK Biobank would disproportionately contain the subjects who were less severely affected. An alternative possibility is that these findings might represent genotyping errors and in a clinical context one might wish to use Sanger sequencing to confirm them but visualisation in IGV did not reveal any obvious problems. Thus, it seems helpful to report these results in order to contribute to a broader view of the potential impact of *HIRA* variants.

Funding

This work was carried out in part using resources provided by BBSRC equipment grant BB/R01356X/1.

Conflicts of interest

The author denies any conflict of interest.

Ethics approval

UK Biobank obtained ethics approval from the North West Multi-centre Research Ethics Committee which covers the UK (approval number: 11/NW/0382). 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).

Consent to participate

UK Biobank obtained informed consent from all participants.

Availability of data and material

The raw data is available on application to UK Biobank. Detailed results are not provided in order to protect confidentiality.

Code availability

Code and scripts use to perform the analyses are available at *https://github.com/davenomiddlenamecurtis*.

Authors' contributions

DC conceived and carried out the analyses.

References

Adzhubei, I., Jordan, D.M., Sunyaev, S.R. (2013) Predicting functional effect of human missense mutations using PolyPhen-2. Curr. Protoc. Hum. Genet. 7 Unit7.20.

Curtis, D. (2012) A rapid method for combined analysis of common and rare variants at the level of a region, gene, or pathway. Adv Appl Bioinform Chem 5, 1–9.

Jeanne, M., Vuillaume, M.-L., Ung, D.C., Vancollie, V.E., Wagner, C., Collins, S.C., Vonwill, S., Haye, D., Chelloug, N., Pfundt, R., Kummeling, J., Moizard, M.-P., Marouillat, S., Kleefstra, T., Yalcin, B., Laumonnier, F., Toutain, A. (2021) Haploinsufficiency of the HIRA gene located in the 22q11 deletion syndrome region is associated with abnormal neurodevelopment and impaired dendritic outgrowth. Hum. Genet. 1–12.

Kumar, P., Henikoff, S., Ng, P.C. (2009) Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. Nat. Protoc. 4, 1073–1081.

McLaren, W., Gil, L., Hunt, S.E., Riat, H.S., Ritchie, G.R.S., Thormann, A., Flicek, P., Cunningham, F. (2016) The Ensembl Variant Effect Predictor. Genome Biol. 17, 122.

R Core Team (2014) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Robinson, J.T., Thorvaldsdóttir, H., Wenger, A.M., Zehir, A., Mesirov, J.P. (2017) Variant review with the integrative genomics viewer. Cancer Res.

Szustakowski, J.D., Balasubramanian, S., Sasson, A., Khalid, S., Bronson, P.G., Kvikstad, E., Wong, E., Liu, D., Davis, J.W., Haefliger, C., Loomis, A.K., Mikkilineni, R., Noh, H.J., Wadhawan, S., Bai, X., Hawes, A., Krasheninina, O., Ulloa, R., Lopez, A., Smith, E.N., Waring, J., Whelan, C.D., Tsai, E.A., Overton, J., Salerno, W., Jacob, H., Szalma, S., Runz, H., Hinkle, G., Nioi, P., Petrovski, S., Miller, M.R., Baras, A., Mitnaul, L., Reid, J.G. (2020) Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank. medRxiv 2020.11.02.20222232.

Table 1

Table summarising key phenotypic characteristics of four subjects carrying variants predicted to cause haploinsufficiency of *HIRA*.

ID	A	B	C	D
Variant	chr22:19353473GC>G	chr22:19388543CAG>C	chr22:19356982GA>G	chr22:19351429G>A
Transcript specific annotations				
ENST00000263208.5	frameshift	frameshift	frameshift	stop gained
ENST00000340170.8	frameshift	frameshift	intron	stop gained
Highest qualification	College or University degree	CSEs or equivalent	College or University degree	None, left school at 15
Employment status at assessment	In paid employment or self-employed	In paid employment or self-employed	In paid employment or self-employed	Unable to work because of sickness or disability
Fluid intelligence score [sample mean (SD) = 6.16 (2.16)]	7	5	5	Missing
Neuroticism score [sample mean (SD) = 4.12 (3.27)]	3	4	9	3
Clinical summary	Denied significant mental health problems	Denied most mental health problems but answered "Yes" to "Mood swings", "Miserable", and "Ever depressed" questions	Self-reported depression; reported having seen GP and psychiatrist for depression; taking antidepressant.	Denied significant mental health problems. Reported physical health problems, including back problems.