Reviewer's report

Title: Linkage and exome analysis implicate multiple genes in non-syndromic intellectual disability in a large Swedish family

Version: 0 Date: 08 Apr 2019

Reviewer: Rolph Pfundt

Reviewer's report:

In this paper Carlstrom and co-authors describe a large Swedish family from an isolated environment in which multiple family members suffer from ID. The authors have performed a series of genetic tests on a selection affected and healthy family members. Array analysis for CNV and linkage analysis and subsequent exome sequencing analyse in a subselection of individuals.

The authors present a lot of data and highlight a number of SNVs that they claim are likely related to the phenotype of various affected family members. In my opinion the authors are overinterpreting the results and are presenting relatively common variants that are likely benign.

Two variants presented are likely pathogenic:

1: the deletion in 5q31.2 in patient 304 that contains a part of the KDM3B gene, that was recently presented as a likely disease gene causing ID (Diets et al., Am J Hum Genet. 2019 Apr 4;104(4):758-766 (PMID: 30929739)).

2: the homozygous missense mutation in the SLC17A5 gene in patients 829, 830 and 322. This also presented as such by the authors.

The variants in TPR, ACOT4 and FLNA are likely benign as the frequency of these variants in databases such as gnomAD is simply too high for a phenotype of neurodevelopmental disorders.

-The TPR variant may have an allele frequency that is below the threshold that the authors use for the WES data analysis (0.2 %) but 604 entries in the gnomAD database (and 1 x homozygous) is way too high in my opinion. Especially since the allele frequency is the highest in the Finnish population (0.8%) where this family descents from.
- The FLNA variant may have an allele frequency that is below the threshold that the authors use for the WES data analysis but 26 hemizygous entries in the gnomAD database is way too high in my opinion (22 of which are in the Finnish population where this family descents from).

- The complex ACOT4 variant that is presented seems in fact a combination of various known common variants that are present in high frequencies in the gnomAD database. These are rs35724886 with a frequency of 6% (16 % in Finnish cohort), rs373880503 with a frequency of 6% (14 % in Finnish cohort), and rs80196271 with a frequency of 6.5 % (16 % in Finnish cohort). These variants together form the complex variant that is described by the authors that claim that this variant is not present in the gnomAD database.

With these observations the results in this paper are in my opinion overinterpreted and mainly concern common variants.

Remarks:
The resolution of Figure 1 is very low and the details are hard to see.

On line 48 the number 750 is mentioned, but that should probably only refer to the number of X-linked ID genes.

On line 55 the authors claim that most of the 2500 ID are recessive, but that statement is lacking support by e.g. a reference paper.

The authors refer to variants on the X-chromosome in males as "homozygous" but that should be corrected to "hemizygous".
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?
If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal