Reviewer’s report

Title: A homozygous missense variant in HSD17B4 identified in a consanguineous Chinese Han family with type II Perrault syndrome

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Reviewer: Daniel Lieber

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The authors present an interesting case of familial Perrault Syndrome diagnosed through next-generation sequencing (NGS). The case report also includes an interesting table summarizing several reported cases of Perrault Syndrome due to mutations in HSD17B4. Given the consanguineous pedigree, the nature of the mutation in both affected siblings, and previous reports with highly similar phenotypes and genotypes, indeed it does seem like the homozygous HSD17B4 is a likely causal variant in this family. This case helps expand the scope of genotypes and phenotypes in Perrault syndrome / DBP deficiency. Several specific comments regarding the paper:

1) There are several places where the English could be cleaned up, especially the conclusions section.

2) The methods say a panel of genes were targeted but it appears that whole-exome sequencing (via Agilent SureSelect) was performed on the proband -- were only those genes selected for downstream analysis from the whole exome data?

3) It would be helpful to provide a brief description of the peroxisomal pattern and how it differs from the observed MRI findings.

4) The Supplementary file 1 seems to contain two lists with slightly different column headers.

5) HSD17B4 is occasionally written as HDB17B4. Polyphen is written as Polyphena.

6) The authors may want to make sure they included all reported cases of Perrault syndrome due to HSD17B4 mutations in their comparative table, if that is their intended goal. For example, Lines et al 2014 describes two women with symptoms that may be considered to be Perrault syndrome and McMillan et al 2012 describes a female with Type IV DBP who could be considered to have Perrault syndrome. I assume Perrault syndrome is being limited to adult women here, which is fine, otherwise there are adult males with DBP deficiency who have gonadal dysgenesis (e.g. Lieber et al, 2014).

7) It may benefit the paper to discuss that Perrault syndrome due to HSD17B4 mutations and juvenile-onset DBP deficiency reported in adults may be the same disease or at least part of the same disease spectrum. Perrault syndrome, because it was originally defined as ovarian
dysgenesis, may be restricted to females but gonadal dysgenesis can be found in both male and female adults with juvenile-onset DBP deficiency.

8) How many regions of the genome were found to be homozygous by homozygosity mapping? Were there any other rare, protein-modifying homozygous variants present in the proband in regions overlapping with the homozygosity mapping? The paper states briefly that the HDS17B4 variant is the only "novel" variant, presumably in the regions identified by homozygosity mapping but this brief description could be strengthened.

9) It's unclear whether the Supplementary Timeline is being published as a supplement but I don't think it is necessary as long as all the details are in the manuscript.

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.

Yes

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

Yes

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:

Needs some language corrections before being published

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