Reviewer’s report

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

Version: 1 Date: 22 Jun 2017

Reviewer: Paul Lockhart

Reviewer’s report:

The reviewer thanks the authors for taking into consideration previous comments and formulating a well thought out response. The manuscript is considerably improved.

The major point that remains unclear is the classification of the case as type II Perrault syndrome and naming as such in the title.

The authors state that "…PRLTS due to HSD17B4 mutations and juvenile-onset DBPD reported in adults may be the same disease or part of the same disease spectrum." However, while they describe this case as being type II PRLTS, it is not clear that there is adequate evidence to do so.

It is likely that type II PRLTS and juvenile-onset DBPD represent a spectrum of one disease. As the cardinal manifestations of PRLTS do not include additional neurologic features, but those of juvenile DBPD do, it may be more prudent to diagnose these and similar cases as subcategories of DBPD rather than as a subcategories of PRLTS (as Amor et al. 2016 and Matsukawa et al. 2017 have done). Please also note Matsukawa et al. 2017 described an individual with compound heterozygous mutations in the dehydrogenase domain as having juvenile-onset DBPD surviving until adulthood.

A clearer distinction between juvenile-onset DBPD and type II PRLTS within the Ms could provide additional support for the assertion of this case being type II PRLTS. This comparative could include a discussion on how each case reviewed in the Ms was classified, as this is currently not clear. For example, on Page 12 - Line 19, the authors state "However the VLCFA in some DBPD patients could be normal as well [2, 25]" and cite Amor et al. 2016. However, in their response to review, the authors state that "…we considered them as PRLTS or uncertain cases so not to comment them in the juvenile DBPD part." Minor revisions that further clarify the definition of and distinction between juvenile-onset DBPD and type II PRLTS would strengthen the author's assertions.

Other points

* Page 2 - Line 3 and Line 8 - the cardinal features of PRLTS include sensorineural hearing loss in both sexes and primary ovarian insufficiency in females

* Page 2- Line 14 - Unaffected carriers not heterozygous
* Page 7 - Line 11 - Please state the amount of protein loaded per sample

* Page 7 - Line 15 - Please state the antibody catalogue numbers and dilution or concentration used

* Page 12 - Line 6 - The sentence should read "…most significant characteristics of DBPD types I, II and III."

* Page 12 - Line 8 - The sentence should read "In DBPD types I, II and III…"

* Page 12 - Line 24 "Some common manifestations of DBPD were not found in this case". What were these?

* Page 13 - Line 12 "Based on this case, we summarized definite or probable PRLTS cases involving HSD17B4 mutations" What criteria determined whether a case was a definite or probable PRLTS case?

* Please remove the priority claims associated with 'first' eg p5 Line 4, p10 Line 17, p14 Line 2. It is sufficient to state 'a' Chinese family with …. 

* Table 1 - Molecular and clinical details for PRLTS patients with HSD17B4 mutations. The authors should include the individuals described in the following reports in Table 1 if they consider them to be PRLTS secondary to HSD17B4 mutations


* Figure 5 - Please describe the statistical methods employed and show error bars

**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?**
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