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: Paul Lockhart

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The authors describe two Chinese sisters from a consanguineous union with a homozygous c.244G>T/p.(A82S) mutation in HSD17B4 and clinical features stated to be consistent with type II Perrault syndrome: OMIM #233400.

The proband presented with an ataxic gate, dysarthria, mild hyertonia in lower limbs, hyperactive deep tendon reflexes, mild intellectual impairment, nystagmus on lateral gaze, hypermetric saccades and secondary amenorrhoea. Poor performance was also noted on finger-nose tests, alternating movement tests and straight-lying walking assessment. The proband's sister had a similar clinical presentation, albeit primary amenorrhoea. Brain imaging in the proband showed moderate cerebellar atrophy. Audiometric examination revealed bilateral sensorineural hearing deficit for higher frequencies. Pelvic ultrasonography showed a small uterus with endometrial stripes and ovarian dysgenesis. Biochemical analyses detected elevated luteinizing hormone and follicle stimulating hormone with low estradiol levels. VLCFA levels were normal and there was no obvious dysmorphology.

The authors suggest that this case report describes a kindred with Perrault syndrome type 2. However, the clinical descriptions do not appear to support this diagnosis over juvenile DBP deficiency. Perrault syndrome is typically characterised by sensorineural deafness in both sexes and primary ovarian insufficiency in females. In contrast, juvenile DBP is characterised by childhood/adult sensorineural deafness, ataxia (often with cerebellar atrophy) and hypergonadotropic hypogonadism.

The assertion by the authors that VCLFA levels can be used to discriminate between Perrault syndrome and DBP deficiency may be generally accurate for infantile DBP deficiency but not for the juvenile form. Indeed the spectrum of clinical features seems very much to reflect juvenile DBP deficiency. This reviewer was a contributor to a recent article that summarised the clinical features of all reported cases of juvenile DBP deficiency and described 5 additional patients from 3 families (Amor et al 2016 Neurol Genet). While the authors comment on one study describing juvenile DBP (McMillan 2012), they do not appear aware of >5 recent publications describing juvenile DBP in greater detail.

In the absence of additional compelling evidence to support the authors claim of the differential diagnosis it is hard to advocate for publication of this case report as it is currently written. Given the in silico classification of the variant as a VUS, this manuscript would be strengthened by some functional data (eg a western blot) showing altered steady state levels of the protein.
Minor comments

1. Mutation description - base variant description on NM_000414.3 instead of NM_001199292.1 to allow simple genetic comparisons to be made in Table 1.

   a. NM_000414.3(HSD17B4_i001):p.(Ala100Ser) instead of NM_001199292.1(HSD17B4_i001):p.(Ala82Ser)

2. Why have the authors not listed PRLTS5 (OMIM: #616138), caused by mutation in the C10orf2 gene (OMIM: #606075) on chromosome 10q24, as a cause of Perrault syndrome?

3. All rare variants that were tested for segregation should be listed in a supplementary table. All variants identified in genes associated with Perrault syndrome should also be included in the supplementary table. Please also include the coverage for each variant.

4. The authors should include the results from the in silico algorithms utilized to assess variant pathogenicity.

5. The Mini-Mental State Examination version should be stated and the score should have a descriptive category, e.g. normal cognition, to make interpretation easier.

6. How was parental consanguinity confirmed? Any evidence should also be included. Homozygosity analysis of the WES data could provide additional 'linkage' support for HSD17B4 and potentially exclude other loci associated with Perrault syndrome.

7. Double lines denoting parental consanguinity should be drawn in the pedigree.

8. The hearing of the proband's sister was described as a little better. How was this conclusion reached? Were audiometric examinations undertaken? These results should be included if so.

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.

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

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Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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