Reviewer's report

**Title:** Next generation sequencing with copy-number-variant detection expands the phenotypic spectrum of HSD17B4-deficiency

**Version:** 3  
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**Reviewer:** Gregory M Enns

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Lieber and colleagues report an interesting case of progressive cerebellar ataxia in whom targeted exome sequencing revealed mutations in HSD17B4, the gene coding for D-bifunctional protein. This case expands our understanding of the phenotype of D-bifunctional protein deficiency and also highlights the clinical utility of targeted exome sequencing followed by the use of computational algorithms for CNV detection for the evaluation of patients with suspected mitochondrial disease. This is an interesting, well-written manuscript and my comments are minor.

**Minor essential revisions:**

Because of the importance of the fatty acid results in establishing the biochemical effects of the mutations in HSD17B4, it would be helpful to include the actual values in the text along with normal ranges.

It is often difficult to obtain accurate blood pyruvate levels, so perhaps it would be better to characterize the level as “essentially normal”. The minimal elevation of the pyruvate just beyond the normal range is unlikely to have any clinical significance.

The authors state that three other genes that have been linked to Perrault syndrome are present in MitoCarta and presumably these genes were also part of the targeted exome analysis (and no significant variants identified). If so, please state explicitly.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.