Author's response to reviews

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

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Author's response to reviews: see over
February 20, 2014

Dear Editors:

Please find enclosed our revised manuscript (MS 1031027774112552) “Next generation sequencing with copy-number-variant detection expands the phenotypic spectrum of HSD17B4-deficiency” for consideration for publication as a case report in *BMC Medical Genetics*. We appreciate the positive and constructive feedback from the reviewers, which we have incorporated into the revision.

Here is our point-by-point response:

Reviewer 1:

*Minor essential revisions*

1) We have included the values and reference ranges for fatty acid testing in the main text. (Line 102-107)

2) We have changed the pyruvate test from “mildly elevated” to “essentially normal”. (Line 100)

3) We now explicitly state that the genes previously implicated in Perrault syndrome were part of the analysis. (Line 207)

Reviewer 2:

*Major compulsory revisions*

1) We have included the values and reference ranges for fatty acid testing results in the main text. (Line 102-107). Patient results or lab reference ranges for C26/C22, C24/C22, di- and tri-hydroxycholestanolic acids, and plasmalogen levels were not available.

2) We have added information regarding ETC measurements and have included a supplementary table of ETC testing results. (Supplementary Materials and Table S1)

*Minor essential revisions*

- We have added “peroxisomal defects” to the list of key words. (Line 39)

*Discretionary revisions*

1) We have added the results and methodology for the IQ test. (Line 87) We have kept the developmental milestones in the supplement because we felt it would distract from the main
points of the paragraph in the main text.

2) We have clarified that the “small amounts of lactate” were found through urine organic acid analysis (Line 101). We deleted the sentence in the supplementary materials stating that small/trace amounts of succinic and 2-oxoglutaric acids were found.

3) We have noted in line 205 that HSD17B4 is found in MitoCarta, an inventory of mammalian mitochondrial proteins. We have performed a computational analysis as to whether the 5’UTR of the HSD17B4 gene could reveal a mitochondrial targeting sequence which could be generated by alternate splicing, and have not found evidence of this, as there are no potential start codons in the 5’ UTR of either HSD17B4 mRNA isoform (NM_000414, NM_001199292).

4) While a more comprehensive steroid profile analysis is unfortunately not available, we have added a paragraph to the discussion regarding how HSD17B4 deficiency could lead to azoospermia and low testosterone levels. (Line 189-199).

Editors

- We include a statement in the Consent section that states: “Study protocols were approved by the Partners Human Research Committee.”

We believe that our paper represents an important and timely manuscript that will appeal to the broad readership of *BMC Medical Genetics*. We thank you for your time and consideration.

Sincerely,

Vamsi K. Mootha, MD