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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Dear Editors:

Please find enclosed our new manuscript, “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.

In our manuscript, we describe the case of a 35-year-old male patient with a previously undiagnosed syndrome of cerebellar ataxia, peripheral neuropathy, hearing loss, cognitive impairment, and azoospermia. Commercially available genetic testing of 18 different ataxia and mitochondrial disease genes was negative, but biochemical findings in serum, urine, and muscle biopsy pointed to the possibility of a mitochondrial abnormality. Targeted exome sequencing, followed by a computational algorithm to infer copy-number-variants (CNV) from exome data, revealed compound heterozygous mutations in the peroxisomal D-bifunctional protein HSD17B4. Recessive mutations in HSD17B4 are a known cause of peroxisomal D-bifunctional protein deficiency and have recently been reported in two sisters diagnosed with Perrault syndrome, who presented with ataxia, hearing loss, and ovarian dysgenesis. Retrospective review of patient records revealed elevated ratios of pristanic:phytanic acid and arachidonic:docosahexaenoic acid, consistent with a peroxisomal disorder. Due to the phenotypic overlap with previous cases of HSD17B4-deficiency, the predicted severity of the HSD17B4 mutations, and the metabolic evidence of peroxisomal dysfunction, the patient was given a diagnosis of Perrault syndrome (MIM #233400).

Our case report (1) represents the first male with ataxia and infertility due to recessive HSD17B4 mutations and expands the phenotype of Perrault
syndrome, (2) highlights the importance of considering CNVs in the diagnosis of neurological disorders, and (3) points to organelle-cross talk in the pathogenesis of mitochondrial and neurological disease. The paper combines highest-grade clinical evaluation and exome analysis. All coauthors have read and approved the submission to the journal and I certify that the manuscript is not under review at any other publication. Given the growing interest in atypical presentations of orphan diseases and the benefits and limitations of new sequencing technologies, we believe that our paper represents an important and timely manuscript that will appeal to the broad readership of BMC Medical Genetics.

Sincerely,

Vamsi K. Mootha, MD