Reviewer's report

Title: Exome sequencing of a patient with suspected mitochondrial disease reveals multigenic etiology.

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Reviewer: Alexander Malcolm Taylor

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Exome sequencing of a patient with suspected mitochondrial disease reveals multigenic etiology, Craigen et al.

The authors describe an extremely interesting consanguineous family with a patient having clinical features of mitochondrial disease and cerebellar ataxia. The authors carried out exomic sequencing on the patient and both parents. They conclude that the presence of homozygosity for a SETX splice site mutation together with the presence of a missense mutation in the X-linked OCRL gene may have contributed to the patient's clinical phenotype.

Minor essential revisions

1. That the SETX splice site mutation together with the presence of a missense mutation in the X-linked OCRL gene may have contributed to the patient’s clinical phenotype is plausible. I believe that the word likely’ should be inserted in the title to give “Exome sequencing of a patient with suspected mitochondrial disease reveals a likely multigenic etiology”.

2. I am not aware of Senataxin 1 only Senataxin.

3. The pedigree is helpful and interesting, but it would also be helpful to have the mutations in SETX and OCRL in a more accessible and more usual nomenclature using the coding sequence. Eg for SETX I think that it is SETX c.5375-1G>A. This begs the question, not answered here, of whether this mutation results in loss of exon 10 and loss of senataxin protein or expression of a truncated form of the protein. As exon 10 codes for 58aa, such a protein truncation would be detectable.

4. We have to assume that it was because the patient was not available for further clinical investigations (page 13) that these particular procedures were omitted. Both of these would require a cell line to be made from patient material (blood or skin biopsy). To mention this would be helpful.

5. I could not find an indication that serum AFP level was measured in the patient’s blood. The authors rather awkwardly describe the increased level of serum AFP in AOA2 patients as ‘variable increases’. Most would agree that the serum AFP level was invariably increased in AOA2 patients.

Comment

The authors summary is correct, that exome sequencing improves the diagnostic
‘possibilities’ but that some patients will require further clinical and/or functional studies to achieve a complete diagnosis. This is the case here.

**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'