Reviewer's report

Title: Molecular and biochemical characterisation of a novel mutation in POLG1 associated with Alpers syndrome

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Reviewer: Robert W Taylor

Reviewer's report:

The manuscript by Schaller and colleagues describes the biochemical and molecular genetic investigations of a child with Alpers syndrome, documenting a novel, recessive splice site mutation in the POLG gene. The experimental data are clear and convincing, and I believe that the case report would be of interest to the field, thus documenting a novel mutation in this gene.

Major Compulsory Revisions:

1. The authors comment in the Background of the Abstract that Alpers patients with the p.A467T mutation in trans with another recessive mutation are mainly male - I wonder whether this has been formally documented in the literature?

2. From the description of the Methods and Results in the text, it appears that the molecular genetic studies were performed first, making a diagnosis of POLG disease, followed up by the assessment of mtDNA copy number and biochemical testing. This is perhaps unusual in the context of much diagnostic testing of patients with suspected mitochondrial disease, in which histochemical and biochemical testing often guides the molecular analysis. Perhaps the authors could just clarify this, although it does seem justified in this case given the characteristic clinical features of Alpers syndrome would advocated POLG gene screening.

3. The biochemical data are nicely presented, showing the marked deficiencies in liver in agreement with the low mtDNA copy number. Was any histochemical analysis of any tissues performed?

4. There is a suggestion in the text that prenatal/CVB testing has been offered to this family as a result of the molecular diagnosis, although no result/data are shown?

Minor Compulsory Revisions:

1. I believe the correct name for the gene is POLG and not POLG1; this should be corrected throughout the text.

2. Page 6, Methods - the authors give the name of authors of a paper [reference 21], although one of these is incorrect. "Birch" should read "Birch-Machin".
3. It would be helpful to have more information on some of the control data given. The respiratory chain data are expressed as a control range for 22 samples, can these activities be represented as mean +/- SD. Likewise, some indication of the number of controls used to establish the control range for mtDNA copy number in different tissues would be helpful. These data could be added, including mean +/- SD, to the appropriate Figure Legend.

Level of interest: An article of importance in its field

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