Reviewer's report

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

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Reviewer: Margherita Milone

Reviewer's report:

This is an interesting case report on a patient with Alpers syndrome carrying a novel splice site mutation in intron 6 and the common p.A467T. The novel mutation results in exon 7 skipping without disrupting the reading frame. MtDNA depletion was detected in muscle and especially in liver. The paper underlines the potential risk of valproate-induced liver failure in POLG-related disorders.

• Major Compulsory Revisions: None
• Minor Essential Revisions

1. Abstract, Background, Sentence before last: “In compound heterozygote patients the p.A467T mutation has been described to be associated with fatal childhood encephalopathy”: The sentence almost implies that p.A467T in compound heterozygosity results only in Alpers, while it can results in other phenotypes too. The authors may want to modify the sentence.

2. Abstract, Conclusions: POLG1 analysis optimizes clinical management. The authors may consider explain how it prevent mitochondrial disorders or delete this statement from the abstract.

3. Discussion, page 10, lines 7-9: It might be cautious to underlines that POLG1 mutations are associated with risk of valproic-induced liver failure without linking this risk to specific mutations.

• Discretionary Revisions: None.

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.