Reviewer's report

**Title:** Pure exercise intolerance and ophthalmoplegia associated with the m.12,294G>A mutation in the MT-TL2 gene: a case report

**Version:** 0  **Date:** 10 Aug 2017

**Reviewer:** Gittan Kollberg

**Reviewer's report:**

Comments on the manuscript "Pure exercise intolerance and ophthalmoplegia associated with the m.12,294G>A mutation in the MT-TL2 gene: a case report."

The authors describe a case with pure myopathy caused by a heteroplasmic mutation in MTTL2 in mitochondrial DNA. They present data from an exercise physiological test of the patient, and they provide confirming and supporting evidence that this mutation is pathogenic. The manuscript is easy to follow and the figures are nice and confirmative for a mitochondrial disorder.

I have some major concerns:

The same mtDNA mutation has been previously reported (Ref #18 - Pulkes et al Neurology 2003) in a patient with almost identical phenotype, but this is not mentioned until in the discussion part of the present report. I think this is important information, which should be mentioned already in the introduction/background. The similarity of the two cases can be discussed later.

The authors' main conclusion of this study is the association between the mutation and the pure myopathy. For me this is more like circular reasoning: "The mutation is only present in muscle and therefore only muscle tissue is affected."

It would be interesting if they instead could speculate WHEN the mutation arose (like in Pulkes et al). If this mutation arose early in the embryogenesis but after the differentiation of the mesoderm, I believe it is interesting that a potentially pathogenic mtDNA mutation reported only twice hitherto, arises sporadically both times, affecting the same tissue, and thus causing the same phenotype.
Minor comments:

Page 2 (Abstract): In the conclusion - change "suggest" to "support"

Page 2 line 27 (Background+ several more times throughout the manuscript): Mitochondrial DNA is most commonly shortened mtDNA and not mDNA

Page 2 line 31 (Background): mtDNA mutations are mostly present in multiple tissues (although in varying amounts), which may be the reason why these cases are so rare …

Page 5 line 4: Reference #9 does not describe the measurement of Lactate/Pyruvate (described in brief in ref #11)

Page 7 (Figure 2) I assume that the sequencing electropherograms are from the Sanger sequencing

Page 7 (Abbreviations) Add "H&E: Hematoxylin and Eosin" to the list

Are the methods appropriate and well described?  
If not, please specify what is required in your comments to the authors.  

Yes

Does the work include the necessary controls?  
If not, please specify which controls are required in your comments to the authors.  

Yes

Are the conclusions drawn adequately supported by the data shown?  
If not, please explain in your comments to the authors.  

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?  
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.  

I am able to assess the statistics
**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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