Reviewer's report

Title: Mitochondrial mosaics in the liver of 3 infants with mtDNA defects

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Reviewer: Christophe Rocher

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Authors still confuse mtDNA heteroplasmy and Cytochrome c oxidase (COX) staining cells heterogeneity. A COX staining mosaic pattern in muscle, due to staining heterogeneity, is found, during diagnosis, with a very low frequency and most of the time, this mosaic pattern is linked with an mtDNA alteration called deletion. An example of this confusion is the reference number 6 in the manuscript cited in the background paragraph. In this article, authors studied an heteroplastic mutation (as most of pathological mutation (base change) in mtDNA) : A3243G and determine heteroplasmy level of this mutation in muscle and single fiber of several patients. But they did not show any data with a COX staining mosaic pattern in muscle, which could be related with heteroplasmy level of the mutation, as proposed by Roels F et al. Moreover, regarding the very few number of real report showing COX staining mosaic pattern in muscle related with an heteroplastic mtDNA mutation (not deletion), it is very surprising to read line 2 of the Background paragraph “…has repeatedly been visualized… ». By all these points, it seems that, authors are not clear with certain mtDNA properties. Maybe, that is why, the question posed by authors is not well defined. Indeed, (i) on one hand by the title, it seems that they want to present 3 novel cases of COX staining mosaic pattern in liver. This is very interesting because for the first time this kind of pattern is associated with Alpers syndrome (2 patients). But unfortunately, article is not written this way. (ii) On the other hand, reading Conclusions paragraph, authors’ goal is to demonstrate that in some cases:

- liver is more informative than muscle : one could expect a complete study on muscle and liver on the same patients and then a comparison between both tissues. This is not the case, because the study of each patient is not complete and therefore it is difficult to compare and then to affirm and propose a new approach for physicians and pediatricians. Such approach has already been done by Sarzi et al (J Pediatr. 2007 May;150(5):531-4, 534.e1-6) on about 50 patients, and even if they do not have information for both muscle and liver for all patients, they have enough patient (about 16) to conclude and proposes something significant.

- COX staining mosaic indicates that mtDNA has to be essayed: As soon as mitochondria are suspected to be involved in the pathology, mtDNA study has to be done. This is done by all centers involved in mitochondrial pathology diagnosis. Because of the low frequency of the mosaic pattern and the lack of relationship between mtDNA mutation heteroplasmy level, mosaic pattern is just an element in the diagnosis of the type of mitochondria pathology and not a key.
Due to the lack of very clear question, manuscript is unclear, not enough focus on one point or another: author do not choose a way to present data either (i) or (ii). Finally author do not emphasize enough the real novelty of their 3 cases (especially both with Alpers Syndrome) and data are not rigorous enough to confirm their assumption on the way how to diagnose mitochondrial defect on liver patients instead of muscle.

Considering all these points, I still consider that author findings are not sufficiently novel and strong to warrant publication.

**Level of interest:** An article of insufficient interest to warrant publication in a scientific/medical journal

**Quality of written English:** Needs some language corrections before being published

**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