Reviewer's report

Title: OPA1-related dominant optic atrophy is not strongly influenced by mitochondrial DNA background

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Reviewer: Valerio Carelli

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This study is aimed at investigating the role that mtDNA genetic background (haplogroup) may play on the pathogenic expression of mutations in the OPA1 gene, responsible for Dominant Optic Atrophy (DOA). The authors report that there is no difference comparing the DOA patients with a sample of French population, concluding that mtDNA haplogroups do not influence OPA1-related DOA.

Major revisions

The issue investigated by the authors is relevant, but difficult in the study design. One first point which is unclear is the pool of patients investigated. In the abstract and in the patient's section of the methods it is stated that the OPA1 patients investigated were 72, even if from 32 unrelated families. However, in both the results and discussion sections there is no mention of the 72 patients, but only of the 32 unrelated probands. This point is of obvious importance, because 32 probands may not produce the required statistical power to disclose an mtDNA haplogroup influence.

On the other hand, the cases that belong to the same family may not necessarily be included. DOA is dominantly inherited, but if the inheritance is from a female the mtDNA haplogroup would obviously remain the same, whereas if the OPA1 mutant allele is inherited from a male the mtDNA haplogroup will change. How the two models have been considered in this study?

Furhtermore, what exactly is the hypothesis of the authors? Do they really believe that the mtDNA haplogroup would be necessary to express the disease like is the case for LHON? Or do they think that the mtDNA haplogroup may influence the clinical expressivity, thus the severity of the disease? In this latter case, a correlation with subcategories of clinical severity scored by precise criteria should be considered, but the number of patients to investigate needs to be higher than 32 probands. It is very unlikely to disclose any relevant effect of mtDNA haplogroups with such a small number of patients analyzed.

The recent association of haplogroup J with LHON suggests that specific clades are responsible for the association. In this study the authors, to compensate for the low number of patients analyzed, adopt the opposite strategy considering four super-haplogroup aggregations.

In the discussion, I would downplay the indication that OPA1-negative DOA are
influenced by mtDNA haplogroups. This study was again based on an insufficient number of patients and the patients may have a heterogeneous genetic basis, given that multiple loci associated with DOA still await for other genes to be discovered.

Minor points
Page 4: the last sentence of the PATIENTS paragraph is unclear
Page 6: again the sentence “This image takes sub-haplogroups into account……..” is unclear

In conclusion, this study has a major weakness in the low number of patients analyzed, thus the conclusions should consider the preliminar nature of these results.

Level of interest: An article of importance in its field

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

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests