Reviewer’s report

Title: Association of the mtDNA m.4171C>A/MT-ND1 mutation with both optic neuropathy and bilateral brainstem lesions

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Reviewer: Ramon Marti

Reviewer’s report:

The manuscript reports the association of the m.4171C>A mutation (so far associated to pure LHON phenotype only) with a combination of LHON and Leigh-like phenotype in a male patient. The mother and one sister had presented only a mild and partially reverted optic phenotype in the past. In this family, the m.4171C>A mutation is associated with a synonymous change in MT-ND1, and with 3 non-synonymous transitions in MT-ND2 and MT-ND6, all of them in homoplasy and in the haplogroup H. These variations are markers of different specific ancient mtDNA sub-haplogroups, but had never been reported in the haplogroup H. The main interest of this case report is the novelty of the overlapping LHON and LS phenotype in association to the m.4171C>A mutation, together with the mtDNA study. These observations suggest that the interaction of these variants in ND genes with the m.4171C>A mutation could contribute to the atypical phenotype in the proband. The report indicates that sequencing the complete mtDNA may help us understand the variability in the clinical presentation often observed in mitochondrial patients, as the authors note in their conclusions.

I only recommend some Discretionary Revisions:

1-I suggest eliminating or reformulating the sentence in the abstract indicating that in silico analysis supports the synergetic role of the variants. According to table 1, the conservation of the affected amino acids is only moderate, and the results obtained from the two software tools used are not fully consistent. Although reporting this information in the results is useful for the readers and it helps to discuss the findings, it is probably not justified to say in the abstract that these weak predictions support the role of the variants.

2-Table 1 presents results of conservation. While the method used to analyze the conservation of the contiguous amino acids has been referenced (ref. 7), the method used to obtain the conservations of the actual amino acids in Eukaryotes, Vertebrates and Mammals should be more detailed (i.e., how many species were included, or refer to a previous described method).

3-Although some clinical laboratories still use mg/dl as units for many biochemical parameters, it is currently more common and probably more recognizable to express the lactic acid levels as mmol/l (or mM).
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