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: Gavin Hudson

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The authors present an interesting case, a patient with Leber's hereditary optic neuropathy who also suffers bilateral brainstem lesions. The conclusion is that the mitochondrial DNA mutation (4171C>A) is the cause of both phenotypes, similar to the effect seen in Leigh-like syndromes.

I have a couple of questions that need to be addressed:

1 - The authors state that the m.4171 variant is present in the proband and mother, as well as an "unaffected sister" - is the unaffected sister negative for LHON as well as the brainstem lesions - if so how do the authors account for the reduced penetrance given the homoplasmic nature of the variant?

2 - On a similar theme the, discussion states that the affected mother and sister only shows optic neuropathy, without brain pathology - again how can the authors account for this variable penetrance?

3 - The brainstem lesions and resultant phenotypes are characteristic of a cerebella based disorder, given the reduction in penetrance (the isolated proband phenotype is potentially autosomal recessive) it would be prudent to exclude common causes of ataxia etc before concluding that the phenotype is caused solely by mtDNA?

Given the frequency of LHON it is possible that the proband is merely unlucky and has coincidentally inherited two different syndromes.

4 - It is interesting that idebenone appeared to reduce the brainstem lesions, however the authors do not indicate why the mother and affected sister were not treated - especially in light of the possible visual recovery seen in the proband?

Level of interest: An article whose findings are important to those with closely related research interests

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