Reviewer’s report

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

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Reviewer: Eduardo Ruiz-Pesini

Reviewer’s report:

In this manuscript, “OPA1-related dominant optic atrophy is not strongly influenced by mitochondrial DNA background” by Pierron et al, the authors test the influence of mtDNA haplogroups on patients with OPA1 mutations and autosomal dominant optic atrophy. The comparison of the mtDNA genetic background between patients and controls do not reveal significant differences. Therefore, the authors conclude that mitochondrial haplogroups are not a strong influence on ADOA expression.

Leber’s Hereditary Optic Neuropathy (LHON) and Autosomal Dominant Optic Atrophy (ADOA) are the most frequent hereditary and primary optic atrophies. LHON is mainly due to one out of three amino acid replacements in mitochondrial ND genes. These mutations greatly decrease the ATP production. However, the penetrance is incomplete. Other factors are required to express the disease and it has been shown that the mitochondrial haplogroup is one of them. Some haplogroups have apparently a lower coupling efficiency for the OXidative PHOSphorylation system (OXPHOS) and, therefore, this will contribute to a lower ATP production. The combination of these two factors in the decrease of the ATP production will enrich the patient population in individuals from these genetic backgrounds. Very interestingly, patients with OPA1 mutations show a decrease in the ATP production and the mitochondrial inner membrane potential. Moreover, it has been recently shown that LHON and ADOA patients share a common mitochondrial uncoupling (Chevrollier et al, 2008). Further, haplogroup J has been shown three–fold over-represented in OPA1-negative ADOA patients (Han et al, 2006). For all these reasons, the question posed by the authors is pertinent. Moreover, it has been correctly defined.

The used methods are appropriate and well described. Data are not particularly sound. OPA1 mutations are probably very pathologic and they are more independent of the influence of other genetic and environmental factors. The manuscript adheres standards for reporting data, although they have not used the accepted nomenclature to design mtDNA mutations (m.14484T>C, not T14484C). Discussion and conclusions are well balanced and adequately supported by the data. The limitations of the work are clearly stated. Probably, the main limitation is the sample size of the patient population. The authors clearly acknowledge works upon they are building (curiously, they forgot to cite one of his interesting jobs, the one from Chevrollier et al, 2008). The title and abstract accurately convey what has been found. The writing is acceptable.
Therefore, and because the previous reasons, I support the publication of this manuscript in your journal. The next recommendations should be considered as discretionary revisions.

Page 3, line 3: They should change neuropathie by neuropathy.
Page 3, last line: Why do they not use the article from Richard et al, 2007? In this article, the authors analyze 1385 French individuals.
Page 4, line24: They should change “…AluI amplification enzyme…” by “…AluI enzyme of an amplicon…”.
Page 6, line 17: The meaning of this sentence (This image ..... Frech people) is not clear.
Page 8, line 20: It is true, the clinical expression of the m.3460G>A pathologic mutation is not influenced by the mtDNA haplogroup J but it has been recently shown that another mitochondrial genetic background, haplogroup U5, is over-represented in patients with this pathologic mutation (Hudson et al, 2007).
Page 18, Table 1: The control region sequence and RFLP analysis is not enough to characterize the patient 1742 as a member of the haplogroup U5. He could also be a member of U4. Please, compare the sequences of the patients 1742 and 1106. The SNP m.16270C>T is not enough to define this individual as a member of U5.

**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