



HAL
open science

Increased mtDNA Copy Number Does Not Protect Against LHON

Josef Finsterer, Sinda Zarrouk-Mahjoub

► **To cite this version:**

Josef Finsterer, Sinda Zarrouk-Mahjoub. Increased mtDNA Copy Number Does Not Protect Against LHON. *Investigative Ophthalmology & Visual Science*, 2018, 59 (1), pp.330. 10.1167/iovs.17-22640 . pasteur-02010317

HAL Id: pasteur-02010317

<https://riip.hal.science/pasteur-02010317>

Submitted on 7 Feb 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

Increased mtDNA Copy Number Does Not Protect Against LHON

We read with interest the article by Bianco et al.¹ about the mitochondrial DNA (mtDNA) copy number in 12 patients with Leber's hereditary optic neuropathy (LHON) and 18 asymptomatic carriers of the primary LHON mutations m.11778G>A and m.3460G>A, respectively. The authors interpreted the increased mtDNA copy number in lymphocytes as a protective effect in LHON mutation carriers.¹ We have the following comments and concerns.

We do not agree with the conclusion that an increased mtDNA copy number is protective against clinical manifestations of a mutation. It is also conceivable that an increased mtDNA copy number represents a nonspecific or compensatory mechanism that has no preventive effect at all. This compensatory effect could be weaker in patients as compared with carriers. Figure 1A nicely shows that the copy number is independent of the heteroplasmy rate, suggesting that with increase of the mtDNA copy number, mutated and wild-type mtDNA proportionally increase. If mitochondria containing wild-type mtDNA and mitochondria containing mutated mtDNA proportionally increase in number, why should this have a protective effect as implicated by the authors? Did the mtDNA copy number correlate with the disease onset or the disease severity? Was the mtDNA copy number measured in different tissues? Possibly, mtDNA copy number is tissue-specific and variable between different tissues.

We do not agree with the statement that LHON is the most common of the mitochondrial disorders (MIDs).¹ Although large-scale epidemiological data about the frequency of specific and nonspecific MIDs are lacking, there are some indications that nonspecific mitochondrial multiorgan disorder syndromes with a frequency of 1:400 are the MIDs most frequently occurring.²

We also do not agree with the notion that mtDNA itself contributes to the copy number and the heteroplasmy rate. The heteroplasmy rate is predominantly influenced by the bottleneck effect during early oogenesis and probably also during mitotic segregation of the mutation in postmitotic tissues. Which is the mechanism by which mtDNA should regulate mtDNA copy number and heteroplasmy rate?

One of the factors that may convert an asymptomatic mutation carrier into a clinically manifesting patient is oxidative stress due to increase in the amount of reactive oxygen species or reduction of the antioxidative defense.³ Did the authors measure oxidative stress and was there a correlation between any of the oxidative stress parameters and the mtDNA copy number? Another factor could be the haplotype.⁴ Did all included patients carry the same haplotype?

Smoking may be a risk factor for the conversion of asymptomatic mutation carrier into patients manifesting with LHON. According to Table 1, only one patient was a smoker. Is it conceivable that this figure is not reliable?

Why did only 2 of the 12 LHON patients receive idebenone? Idebenone has been shown to be beneficial in a few patients with LHON, particularly if given shortly after onset of the clinical manifestations.⁵ In only one of the two patients who received idebenone was the copy number determined. The authors state that the effect of idebenone is mentioned in Table 1; however, we could recognize only the information on who took idebenone and who did not. Only two patients altogether were taking idebenone, but its effect was neither mentioned in the results nor in Table 1.

Overall, this interesting study could be more meaningful if more patients would have been included, if more patients would have received idebenone, if the effect of idebenone would have been reported, and if the mtDNA copy number would have been assessed in more than one tissue.

Josef Finsterer¹
Sinda Zarrouk-Mahjoub²

¹Krankenanstalt Rudolfstiftung, Vienna, Austria; and the ²University of Tunis El Manar and Genomics Platform, Pasteur Institute of Tunis, Tunis, Tunisia.
E-mail: fifigs1@yahoo.de

References

1. Bianco A, Bisceglia L, Russo L, et al. High mitochondrial DNA copy number is a protective factor from vision loss in heteroplasmic Leber's hereditary optic neuropathy (LHON). *Invest Ophthalmol Vis Sci.* 2017;58:2193-2197.
2. Poulton J, Finsterer J, Yu-Wai-Man P. Genetic counselling for maternally inherited mitochondrial disorders. *Mol Diagn Ther.* 2017;21:419-429.
3. Sadun AA, La Morgia C, Carelli V. Leber's hereditary optic neuropathy. *Curr Treat Options Neurol.* 2011;13:109-117.
4. Ridge PG, Maxwell TJ, Foutz SJ, et al. Mitochondrial genomic variation associated with higher mitochondrial copy number: the Cache County Study on Memory Health and Aging. *BMC Bioinformatics.* 2014;15(suppl 7):S6.
5. Gueven N. Idebenone for Leber's hereditary optic neuropathy. *Drugs Today (Barc).* 2016;52:173-181.

Citation: *Invest Ophthalmol Vis Sci.* 2018;59:330.
<https://doi.org/10.1167/iovs.17-22640>

