Do High mtDNA Copy Numbers Truly Prevent LHON Manifestations?

With interest we read the article by Bianco et al. about the contribution of the mutation load and mtDNA copy number on the penetrance of primary Leber’s hereditary optic neuropathy (LHON) mutations in 30 affected patients. We have the following comments and concerns.

A main clinical feature of LHON is reduced visual acuity. However, according to Table 1, only 11 of 30 patients had reduced visual acuity. How to explain this finding? In 7 of the 11 patients, the mtDNA copy number was not determined. Thus, the finding that mtDNA copy numbers are reduced in clinically manifesting LHON patients is based on only four patients, making the interpretation highly questionable. Why were relatives of LHON patients carrying the mutation classified as LHON patients? Did all 30 LHON patients present with edematous, hyperemic optic nerve heads, vascular tortuosity, and telangiectasias? Was the mild phenotype in most patients attributable to the low heteroplasmy rate in most patients?

A penetrance of 71% in male individuals is high, because it is usually regarded as 50% in male individuals. Risk factors are considered to contribute to the penetrance of primary LHON mutations. However, risk factors were reported in only three patients. How to explain this inconsistency? Were risk factors other than alcohol, smoking, or illicit drugs considered? Was the haplotype determined in all patients? Did the authors look for mtDNA polymorphisms or modifying secondary mtDNA mutations as factors influencing the penetrance of primary LHON mutations?

The m.11778G>A usually occurs in the homoplasmic state in LHON patients. However, in the present study only two patients carried this mutation in the homoplasmic form. How to explain this surprising finding? What were the clinical manifestations of the 12 patients who carried the m.11778G>A variant in a heteroplasmic state? Contrary to what is mentioned in the text, heteroplasmy rates ranged from 5% to 95% in Table 1 but not from 8% to 95%. Which is the correct lower limit?

If the increased mtDNA copy number in carriers of LHON mutations indeed represents a compensatory mechanism, it should be explained why those who manifested clinically lost this ability to compensate for the underlying genetic defect. Was the increase in mtDNA copy numbers due to an increase in the number of mitochondria? How to explain that a reduced copy number triggers the development of clinical manifestations? Reduced copy number suggests lower amount of mutation and thus better outcome and milder phenotype. Was the increase in the number of mtDNA copies also found in tissues other than lymphocytes?

According to Table 1, only two patients received idebenone, which has been shown to exhibit a beneficial effect in LHON and is generally recommended as the most effective treatment of LHON. What is the reason for not supplying the other 28 patients with this drug?

Overall, this interesting study requires clarification of a number of inconsistencies and revision of the conclusions. As long as not all factors influencing the penetrance of primary LHON mutations are considered, it cannot be assessed to which degree the mtDNA copy number truly determines the penetrance of primary LHON mutations.

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References

Citation: Invest Ophthalmol Vis Sci. 2017;58:4076.
doi:10.1167/iovs.17-22307