Author Response: Do High mtDNA Copy Numbers Truly Prevent LHON Manifestations?

We appreciate the interest of Prof. J. Finsterer¹ in our recent publication entitled “High Mitochondrial DNA Copy Number Is a Protective Factor From Vision Loss in Heteroplasmic Leber’s Hereditary Optic Neuropathy (LHON)”² published in IOVS.

We would like to clarify some points that required comments.

Mutations in the mitochondrial (mt)DNA associated with LHON are generally homoplasmic and penetrance and severity of visual defects do not appear to correlate with the mutant mtDNA load.³,⁴ Several reports have already described LHON affected subjects harboring heteroplasmic levels of the primary mtDNA mutations in peripheral blood and in other tissues.⁵-¹² In our cohort of LHON patients, we had selected those who harbored heteroplasmic mutation levels, assessed penetrance, and, whenever sufficient DNA was available, we also tested mtDNA abundance. Our research question was to assess whether (1) penetrance is more influenced by heteroplasmy level or by mtDNA abundance and (2) the increase of mtDNA content protects from vision loss in heteroplasmic subjects.

In our article, we already explained that mtDNA copy number could be assessed in five subjects only and discussed that, even in presence of heteroplasmic mutation, it is not at all the reduction of mtDNA copy number in the affected subjects but rather the increase of mtDNA copy number in carriers in respect to the normal controls and affected (P < 0.001 and P < 0.001, respectively; ANOVA test) to be protective from vision loss. We recognized that the mtDNA haplogroup could have played a role (we did not sequence the whole mitochondrial genomes in those subjects), and environmental factors other than those notoriously associated with LHON (and as yet unknown) could have been involved. Certainly, the main topic of the paper, that is, to point out that higher mtDNA content in blood cells discriminates the unaffected mutation carriers (who harbored 5% to 95% mutant mtDNA) from LHON affected and control subjects, was explicit and well in keeping with data reported by others.¹³

It requires further investigation to understand if oral administration of idebenone, already approved in the European Union to treat visual impairment in adolescents and adults with LHON,¹⁴ is also useful in asymptomatic maternally related family members. Also, the pathogenetic significance of mtDNA copy number remains to be investigated. The difference in the mtDNA copy number estimated as mtDNA/nuclear DNA in cells is generally assumed as the measure of mitochondrial number considering that each mitochondrion may contain 2 to 10 copies of mitochondrial genomes.³ As already said, high blood levels of mtDNA copy number reported in unaffected LHON mutation carriers¹⁵ it might indicate that cells carrying the LHON primary mutations organize a response to restore a balance, which is significantly more efficient in those individuals who remain unaffected. Probably, contrarily to what happens in the presence of a severe pathogenic mutation, the overall weak pathogenic potential of LHON mutations leads to a general increase of mitochondrial mass accompanying mtDNA replication with the aim of bypassing NADH-ubiquinone oxido-reductase activity and compensate for the ATP deficit, suggestive of a possible molecular explanation for the variable penetrance of the LHON primary mutations.¹³ Certainly, all these aspects require further study.

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References


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