Penetrance of the LHON Mutation m.11778G>A May Depend on Factors Other Than the Haplotype or Heteroplasmy Rate

We read with interest the article by Khan et al. about the influence of haplogroups on the penetrance and phenotype of the m.11778G>A variant in 146 manifesting and 397 unaffected carriers of the mutation (64 index cases). No association between the mutation and a specific haplogroup was found. We have the following comments and concerns.

We do not agree with the statement in the introduction that Leber’s hereditary optic neuropathy (LHON) is the most frequent maternally transmitted mitochondrial disorder (MID). The references the authors cite to support their statement are more than 10 years old and more recent studies are available that do not support this statement. The most frequent MID is the nonspecific mitochondrial multiorgan disorder syndrome, which does not fit to any of the MIDs tagged with an acronym.

Penetrance may depend on age. Were the 397 unaffected mutation carriers followed up? Did they develop visual disturbance or other possible manifestations of the mutation later in the disease course? Did initially unaffected mutation carriers become affected during follow-up?

The authors mention that heteroplasmcy could be a modifying factor for penetrance. In how many of the manifesting mutation carriers was the mutation present in the homoplastic form and in how many in the heteroplasmic form? Was the heteroplasmcy rate higher in the cohort of the manifesting mutation carriers as compared with the non-manifesting carriers?

How many of the 543 mutation carriers were smokers, are how many were alcohol addicted? Did those with a history of alcohol consumption or smoking more frequently manifest clinically than those with a negative history for smoking or alcohol, as can be expected from previous studies?

How many of the included patients had a positive family history for LHON? Were there index cases with a negative family history for the disease? How many of the manifesting and nonmanifesting mutation carriers were born to consanguineous parents? How many of the mothers of the 64 index cases manifested clinically?

LHON not only manifests in the retinal ganglion cells (RGCs) and the optic nerve but may also manifest in other organs, such as the cerebral, heart, ears, endocrinological organs, bone marrow, arteries, kidneys, or the peripheral nervous system. Were the 543 mutation carriers prospectively investigated for multiorgan involvement and did those who did not manifest in the RGCs or the optic nerve manifest in other organs? Because the penetrance of the m.11778G>A mutation increased with the mutation load, it would be interesting to know if the number of affected organs increased with increasing heteroplasmy rate.

Pathogenicity of secondary LHON mutations, as listed in Table 4, should not be assessed by in silico methods but rather according to techniques recommended by the American Society of Human Genetics. How many of the variants listed in Table 4 scored >11 on the Yarham score to be identified as definitively pathogenic? Single-fiber and cybrid studies are the gold standard for assessing a variant as pathogenic. In how many of the variants listed in Table 4 were these investigations carried out?

Overall, this interesting study could profit from providing additional data about multimodal involvement, follow-up investigations, and other family members. The relation between severity of phenotype and heteroplasmy rate should be provided.

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