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Frequency of Primary LHON Mutations in Northern India

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Letter to the Editor

In a recent study by Mishra et al. the genetic background of 40 patients with Leber's Hereditary Optic Neuropathy (LHON) from Northern India was investigated [1]. Eleven of the 40 patients (27.5%) were found to carry the primary LHON mutation m.11778G>A [1]. In one family, two primary LHON mutations, m.11778G>A and m.14484T>C, were found in the proband and his mother respectively [1]. The authors concluded that the m.11778G>A variant is more frequent among the Indian population than other primary LHON mutations [1]. We have the following comments and concerns. During recent years it turned out that Mitochondrial Disorders (MIDs) including LHON are not necessarily mono-organ diseases but rather progressive multisystem disorders [2]. Affected organs / tissues other than the retinal ganglion-cells and optic nerve include the Central Nervous System (CNS) (psychomotor delay, dementia, epilepsy, leukoencephalopathy, Posterior Reversible Encephalopathy Syndrome (PRES), migraine, chorea, ataxia), the ears (hypoacusis), endocrine organs (diabetes, thyroid dysfunction, parathyroid dysfunction, pituitary adenoma), the heart (left ventricular hypertrabeculation / noncompaction, dilated cardiomyopathy, supraventricular and ventricular arrhythmias, syncope, angina, Sudden Cardiac Death (SCD)), the bone-marrow (anemia), arteries (aortic stiffness), the kidneys (renal insufficiency), or the peripheral nerves (neuropathy) [2]. Thus, we recommend prospectively investigating the 40 patients for subclinical or mild manifestations of a multisystem disease (Mitochondrial Multiorgan Disorder Syndrome (MIMODS)). Usually, a single, primary, homozygous LHON mutation is sufficient for phenotypic expression [3]. Interestingly, in one family two primary LHON mutations (m.11778G>A, m.14484T>C) were found. Were both variants present in the homozygous form, was there compound heterozygosity, and were both variants pathogenic? Was the phenotype more severe than in the other patients who carried only a single mutation? Which were the heteroplasmy rates of the mtDNA variants found in the 40 included patients? We recommend to investigate the cohort in a future study for the following points: how often were the mutations detected in the 40 patients *de-novo* and how often

inherited; how many of the parents of those with a genetic diagnosis also carried a mutation; did any of the parents of the 40 included patients manifest with LHON or other clinical manifestations of a MID; were the parents systematically investigated for clinical or subclinical MID? There are indications that visual impairment spontaneously resolves in some LHON patients, particularly in those carrying the m.11778G>A variant [4]. In a future study the authors could address the question in how many of the patients carrying the m.11778G>A variant resolution of visual impairment was observed over time. Recently, treatment with idebenone (Raxone®, 900 mg/d) has been approved by the European Medicine Agency (EMEA) for treating LHON patients with acute visual loss due to one of the three primary LHON mutations [5]. In a future study the authors could address the questions how many of the included patients were regularly taking idebenone, in which dosage they were taking idebenone, and if they profited from the treatment? This interesting study could be more meaningful if the included patients would be investigated in a future study for involvement of organs other than the eyes and the optic nerve, for heteroplasmy rates, for haplogroups, and for clinical and genetic manifestations in first-degree relatives. A more widespread discussion about the phenotype and the genetics may stimulate further research to answer at least some of the open questions.

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