Case Reports in Ophthalmology

Case Rep Ophthalmol 2023;14:419–420
DOI: 10.1159/000531387
Received: April 18, 2023
Accepted: May 18, 2023
Published online: September 5, 2023

Letter

Pathogenicity of Variant m.13528A>G in *MT-ND5* in Leber's Hereditary Optic Neuropathy Is Unsupported

Josef Finsterer[a] Sounira Mehri[b]

[a]Neurology and Neurophysiology Center, Vienna, Austria; [b]Biochemistry Laboratory, LR12ES05 "Nutrition-Functional Foods and Vascular Health", Faculty of Medicine, Monastir, Tunisia

Dear Editor,

With interest we read the article by Pandya et al. [1] on a 57-year-old male who was diagnosed with Leber's hereditary optic neuropathy (LHON) due to the variant m.13528A>G in *MT-ND5*. Although the patient did not receive idebenone, visual acuity improved by the 24-month follow-up [1]. The study is excellent but has limitations that are cause of concerns and should be discussed. The CARE Checklist has been completed by the authors for this report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531387).

We disagree that the variant m.13528A>G in *MT-ND5* was causative. The variant has not previously been reported to definitively cause LHON or another syndromic or non-syndromic mitochondrial disorder. The argument that m.13528A>G is really responsible for LHON is not supported by the literature. The variant reported by Batandier et al. was m.13528G>A but not m.13528A>G [2]. The patient described by Petruzella et al. [3] carried not only the variant m.13528A>G but also five other variants, making it difficult to judge which of them was causative. No functional or biochemical studies were performed to confirm the pathogenicity of the variant. The heteroplasmy rate was 100%, indicating that the variant may not have been pathogenic. No studies have been performed to confirm respiratory chain complex-I deficiency. None of the first-degree relatives were tested for the *MT-ND5* variant. Documentation of the variant in other family members and segregation with the phenotype would strongly support the assumption that the variant was pathogenic.

The diagnosis LHON is not well secured. LHON is usually diagnosed by ophthalmologic examination, optical coherence tomography, and fluorescence angiography, showing early leakage and late pooling and reduction of the parafoveal superficial capillary plexus and the radial peripapillary capillary (RPC) network [4, 5], but the index patient had no retinal angiography. The diagnosis LHON also does not ideally match the patient's age. LHON begins

Correspondence to:
Josef Finsterer, fifigs1@yahoo.de

before age 20 years in the majority of cases, with an upper limit of age 50 years. The family history is negative for LHON, and there is no segregation of the variant with the phenotype.

A limitation of the study is that HbA1c values were not provided. Since the patient was diabetic but did not take an anti-diabetic medication, it is crucial to know if blood sugar was well controlled or not. A vegetarian diet is no guarantee that blood sugar will be normal. The dietary habits of the index patient should be specified.

Acute ischemic optic neuropathy has not been ruled out. The patient had an increased cardiovascular risk (alcohol, smoking, diabetes, and age). Therefore, we should know whether atherosclerosis was found on carotid ultrasound, coronary angiography, or ultrasound of peripheral arteries.

Before claiming the variant m.13528A>G as causative of LHON, functional, biochemical, and genetic studies must be performed. In the absence of evidence of respiratory chain complex-I deficiency, the variant cannot convincingly be accounted for LHON. However, the clinical diagnosis of LHON cannot be overlooked, and the variant found cannot currently be ruled out as the cause.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding Sources

No funding was received.

Author contributions

J.F.: design, literature search, discussion, first draft, critical comments, and final approval. S.M.: literature search, discussion, critical comments, and final approval.

References

1 Pandya BU, Vosoughi AR, Jhaveri A, Micieli JA. A rare ND5 mutation causing leber's hereditary optic neuropathy. Case Rep Ophthalmol. 2023;14(1):99–103.
2 Batandier C, Picard A, Tessier N, Lunardi J. Identification of a novel T398A mutation in the ND5 subunit of the mitochondrial complex I and of three novel mtDNA polymorphisms in 2 patients presenting ocular symptoms. Hum Mutat. 2000;16(6):532.
3 Petruzzella V, Carrozzo R, Calabrese C, Dell'Aglio R, Trentadue R, Piredda R, et al. Deep sequencing unearths nuclear mitochondrial sequences under Leber's hereditary optic neuropathy-associated false heteroplasmic mitochondrial DNA variants. Hum Mol Genet. 2012;21(17):3753–64.
4 Yu-Wai-Man P, Chinnery PF. Leber hereditary optic neuropathy. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, et al, editors. GeneReviews® [internet]. Seattle (WA): University of Washington, Seattle; 2000 Oct 26. p. 1993–2023 [updated 2021 Mar 11].
5 Yu J, Xu H, Huang Y, Gu R, Zong Y, Zhu H, et al. Changes in retinal perfusion in leber's hereditary optic neuropathy: an optical coherence tomography-angiography study. Ophthalmic Res. 2021;64(5):863–70.