Case Reports in Ophthalmology

Case Rep Ophthalmol 2023;14:665–666
DOI: 10.1159/000535021
Received: September 27, 2023
Accepted: November 2, 2023
Published online: November 29, 2023

Letter

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

Bhadra U. Pandya[a] Amir R. Vosoughi[b] Aaditeya Jhaveri[a]
Jonathan A. Micieli[c, d, e]

[a]Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [b]Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada; [c]Department of Ophthalmology and Vision Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [d]Kensington Vision and Research Centre, Toronto, ON, Canada; [e]Department of Ophthalmology, St. Michael's Hospital, Unity Health, Toronto, ON, Canada

We thank Finsterer and Mehri [1] for their interest in our case report describing a 57-year-old male patient with the m.13528A>G, p. (Thr398Ala) mutation at the ND5 gene diagnosed with Leber hereditary optic neuropathy (LHON). The CARE Checklist has been completed for the case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535021).

The assertion that "the variant reported by Batandier et al. [2] was m.13528G>A" by the authors is incorrect as the mutation was indeed described as 13528A>G by Batandier et al. [2], consistent with what we reported in our case report. This mutation was present at 100% homoplasmy in our patient, and moreover, McKenzie et al. [3] and Petruzzella et al. [4] reported this mutation to be homoplasmic. Therefore, the assertion that "the heteroplasmy rate is 100%" by Finsterer and Mehri [1] is inaccurate.

McKenzie et al. [3] analyzed the m.13528A>G mutation in a patient with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, and demonstrated (I) increased lactate production and (II) decreased mitochondrial membrane potential, resulting in complex I dysfunction. Petruzzella et al. [4] performed an elegant biochemical analysis in an LHON patient with this mutation where they demonstrated (I) an increase in reactive oxygen species formation and (II) complex I deficiency as characterized by a decrease in adenosine triphosphate production. We acknowledge that neither study definitively implicates the m.13528A>G mutation in causing LHON, but it is inaccurate to assert that there is "an absence of evidence of respiratory complex-I deficiency" in the context of this mutation. We agree that further biochemical studies are warranted

Correspondence to:
Jonathan A. Micieli, jmicieli@kensingtonhealth.org

to confirm pathogenicity. We agree that the patient's age is atypical for most LHON cases; however, later onset of LHON still occurs, and smoking and alcohol consumption – both of which were present in our patient – have been implicated as important risk factors for triggering LHON [5].

Finsterer and Mehri [1] are inaccurate in their clinical assessment of our patient. This patient had slowly progressive vision loss over 3 months. This is not consistent with anterior ischemic optic neuropathy, which presents with sudden vision loss and is usually unilateral. Moreover, assessment of carotid stenosis is not useful in patients in anterior ischemic optic neuropathy [6]. HbA1c values are irrelevant as this patient's presentation is not consistent with diabetic retinopathy or any other eye disease associated with diabetes. Furthermore, the diagnosis of LHON is a clinical one and does not rely on OCT or IVFA. It is worth noting that the fundus exam is normal in up to 50% of patients with LHON [7].

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Funding Sources

No funding was provided for this study.

Author Contributions

Conception and design, acquisition of data, analysis and interpretation of data, preparation of the manuscript, and final approval of the completed manuscript: Bhadra U. Pandya, Amir R. Vosoughi, Aaditeya Jhaveri, and Jonathan A. Micieli.

References

1 Finsterer J, Mehri S. Pathogenicity of variant m.13528A>G in MT-ND5 in Leber's hereditary optic neuropathy is unsupported. Case Rep Ophthalmol. 2023;14(1):419–20.
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 two patients presenting ocular symptoms. Hum Mutat. 2000;16(6):532.
3 McKenzie M, Liolitsa D, Akinshina N, Campanella M, Sisodiya S, Hargreaves I, et al. Mitochondrial ND5 gene variation associated with encephalomyopathy and mitochondrial ATP consumption. J Biol Chem. 2007;282(51):36845–52.
4 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.
5 Dimitriadis K, Leonhardt M, Yu-Wai-Man P, Kirkman MA, Korsten A, De Coo IF, et al. Leber's hereditary optic neuropathy with late disease onset: clinical and molecular characteristics of 20 patients. Orphanet J Rare Dis. 2014;9:158.
6 Fry CL, Carter JE, Kanter MC, Tegeler CH, Tuley MR. Anterior ischemic optic neuropathy is not associated with carotid artery atherosclerosis. Stroke. 1993;24(4):539–42.
7 Fraser JA, Biousse V, Newman NJ. The neuro-ophthalmology of mitochondrial disease. Surv Ophthalmol. 2010;55(4):299–334.