Novel potential nuclear genetic modifier in Leber Hereditary Optic Neuropathy in Wolfram Syndrome-associated variant WFS-1 c.799G>A

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Introduction

Leber Hereditary Optic Neuropathy (LHON) is a maternally inherited optic neuropathy that occurs due to mitochondrial dysfunction. The cause of variation in penetrance remains largely unknown. Usually bilateral optic atrophy becomes evident and stable blindness develops, with 70% of eyes progressing to BCVA worse than 6/60 Snellen within 3 months.

Presentation of LHON typically occurs in young adulthood, with bilateral painless subacute loss of vision. One retrospective study demonstrates that over 95% of LHON pedigrees are associated with one of three mtDNA mutations, including G3460A, G11778A, and T14484C, which affect complex I of the mitochondrial respiratory chain.

We aim to investigate patients with LHON and their unaffected carrier relatives, including genotyping with a panel of potentially relevant genes, and functional and structural testing.

Methods

We prospectively evaluated a cohort of LHON patients and their asymptomatic carrier relatives (n=28), including clinical history, examination, and genetic sequencing including full mitochondrial genome (37 genes), and a nuclear gene panel relevant to neuro-ophthalmology (56 genes).

Vision-related quality of life was assessed via the National Eye Institute's Visual Function Questionnaire 25 (NEI VFQ-25), with the 10-Item Neuro-Ophthalmic Supplement.

Optic nerve function tests included pupil examination, Ishihara colour vision testing, Octopus visual field, and electrophysiology including visual-evoked potential and electroretinogram. Dilated fundus examination was performed with photography, optical coherence tomography (OCT), OCT angiography (pictured below), and autofluorescence.

References

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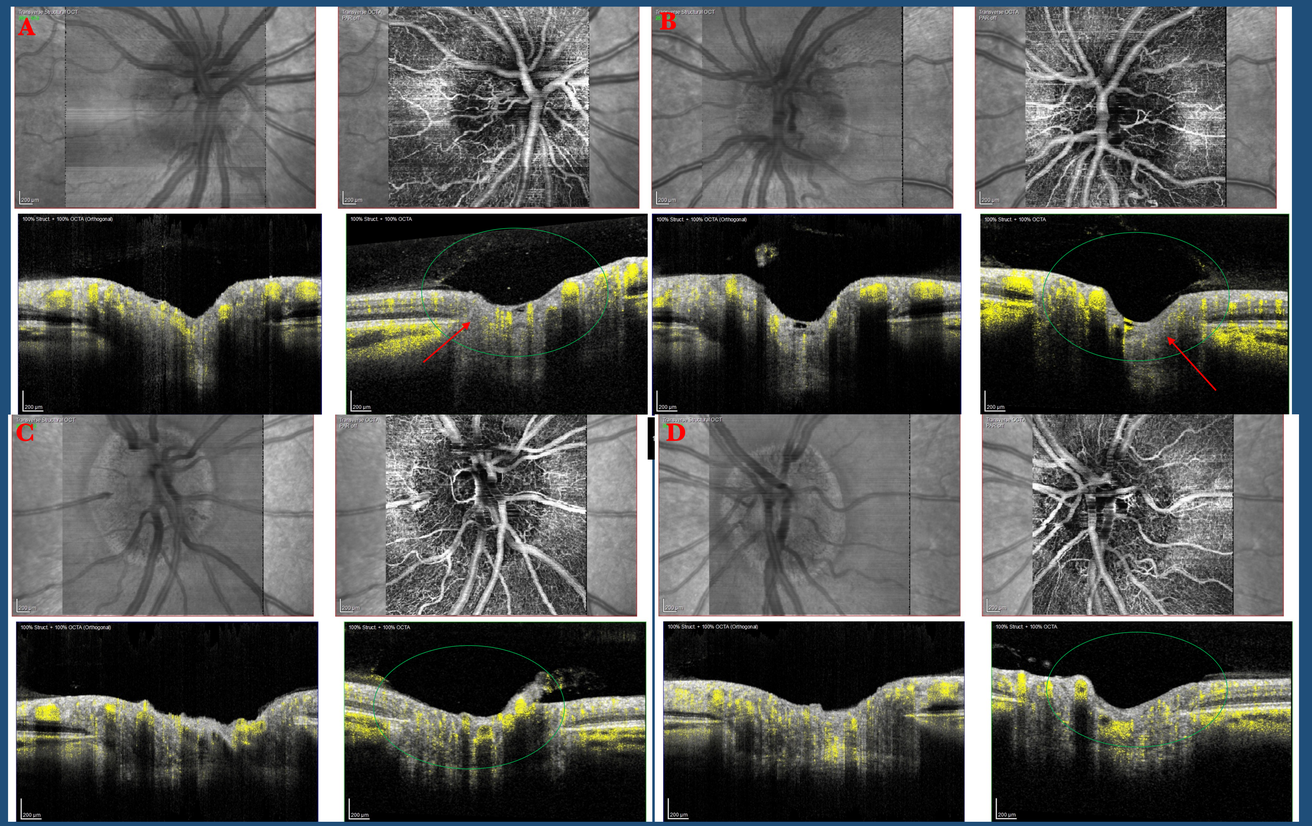


Figure: OCT angiography (OCTA) images of the optic nerve head of the right (A) and left (B) eyes of a patient affected by LHON who carries the variant WFS-1 c.799G>A, and also corresponding images of the right (C) and left (D) images of his unaffected carrier mother. The yellow overlay represents the OCTA signal, caused by intravascular motion of red blood cells, on the background structural OCT. The region of interest is circled in green in these images, where a reduced vascular density is highlighted by red arrows in A and B, the temporal region of the optic nerve head, relative to the same areas in images C and D.

Results

The median best corrected visual acuity (BCVA) for LHON-affected individuals was reduced to LogMar 1.7 (n=13), and for asymptomatic carrier relatives was normal at 0.1 (n=15).

The LHON-causing mutation were confirmed as mt. G11778A for 77% (n=10), T14484C (n=1), and G3460A (n=1), and in one patient there was no mutation identified.

Potential disease modifying nuclear genetic variants identified included WFS1, and POLG, in these cases the BCVA was well preserved at 0.3, and reduced at 1.6 respectively.

Electrophysiology investigation revealed a non-recordable visual evoked response (VER) bilaterally in 77% (n=10), a lengthened VER in 92% (n=12) of those affected by LHON.

OCT angiography revealed temporal papillary microangiopathy in LHON, see Figure.

Discussion

In this cohort visual acuity was poor in most of those affected by LHON (median LogMAR BCVA 1.7), but was relatively well preserved at 0.3 in an individual who was heterozygous for WFS1 799G>A, a variant of uncertain significance. This variant has been described together with WFS1 1294C>G in a patient with a diagnosis of Wolfram syndrome. Wolfram syndrome is known as DIDMOAD syndrome for its most common features (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness).

There is evidence on OCT angiography of micro-angiopathy affecting the optic nerve head of LHON-affected individuals, relative to asymptomatic relatives.

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