



Relative preservation of the extramacular retina in *LCA5*-associated Leber congenital amaurosis

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ABSTRACT

Leber Congenital Amaurosis caused by mutations in *LCA5* (*LCA5*-*LCA*) represents one of the most severe molecular forms of inherited retinal degenerations, even within the *LCA* disease spectrum. A retina-wide retinal degeneration with preservation of photoreceptors limited to central retina, near the foveal center, is the expected phenotype in various forms of *LCA*, including *LCA5*-*LCA*. In this report large areas of relatively preserved photoreceptors in the midperipheral and peripheral retina were documented with spectral domain optical coherence tomography and with fundus autofluorescence in a 13-year-old patient with *LCA5*-*LCA*. The findings raise the possibility of relative structural preservation in the peripheral retina in the setting of severe vision in *LCA5*-*LCA* and other molecular forms of *LCA*, regions that may become additional or alternative regional targets for gene therapies delivered by subretinal injections.

1. Case report

A 13 year-old girl diagnosed with Leber Congenital Amaurosis (*LCA*) caused by homozygous null mutations in *LCA5* (Q421X:c.1263C>T) underwent a comprehensive eye examination and multimodal imaging.¹ Visual acuity was hand motion in each eye with hyperopia and a pendular nystagmus (right eye, +6.25, left eye, +5.25). There had been only minimal changes in vision since childhood. She is otherwise healthy. ERGs were undetectable from an early age. Rod-mediated sensitivities by full-field sensitivity testing (FST), barely detectable at age 11 (~5 log units of sensitivity loss), were now non-detectable (Uyhazi et al. 2020, Patient 2).¹ FSTs performed with the same methodology, but in the light-adapted state (100 cd.m⁻² white background) at age 13 confirmed loss of rod vision and residual cone-mediated sensitivities, abnormally reduced by ~2 log units (+0.4 log cd.s.m⁻², 637 nm stimulus, 4 ms) compared to normal (normal mean ± 2SD = -1.93 ± 0.50 log cd.s.m⁻²; n = 8). On fundus exam there were retinal pigment epithelium (RPE) changes throughout but better appearance of the temporal midperiphery, peripheral nasal retina, and the foveal center (Fig. 1A, to the right of asterisk).¹ In the left eye, a vitreous cyst was visualized anterior to the optic disc (Fig. 1A, short arrow). Wide angle

short-wavelength fundus autofluorescence (SW-FAF) showed an oval area of hypo-autofluorescence outlined by near normal autofluorescence in the nasal midperiphery and by mottled fluorescence in temporal retina. There is overall hypoautofluorescence on near infrared autofluorescence (NIR-FAF) that contrasts against a band of clearly detectable SW-FAF signal in temporal retina that tracks all the way to the nasal midperipheral retina, and against a small island of detectable NIR-FAF at the foveal center (Fig. 1B). The pattern is reminiscent to that observed in some cone rod dystrophies and supports the presence of a patent but demelanized retinal pigment epithelium (RPE). Spectral domain optical coherence tomography (SD-OCT) through the fovea showed detectable outer nuclear layer and a small juxtafoveal segment where the outer limiting membrane and structures in the outer retina (inner segment ellipsoid and apical RPE) were clearly visible (Fig. 1C, Section a, arrow). A cross-section through the nasal midperiphery similarly demonstrated detectable photoreceptors, including signals originating from the inner/outer segment and the RPE, co-localizing with the region of preserved SW-FAF (Fig. 1C, Section b, arrow).

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2. Discussion

LCA5-LCA represents one of the most severe molecular forms of inherited retinal degenerations, even within the LCA disease spectrum. A retina-wide retinal degeneration with better preserved photoreceptors within the central retina is the expected phenotype in various forms of LCA, including LCA5-LCA.¹⁻³ Detection of retinal photoreceptors and of a structural-functional dissociation in LCA5-LCA and recent proof-of-concept studies that demonstrated rescue of the degeneration in the mouse model of the disease raised hopes for treatment.¹⁻³ Documentation of treatable photoreceptors over large expanses of retina that typically escape documentation by conventional retinal imaging, or due to the complexities of imaging patients with severe vision loss and nystagmus, adds those regions as additional or alternative targets for gene therapies delivered by subretinal injections.

3. Conclusion

In this report we demonstrate large areas of potentially treatable retina in LCA5-LCA, a severe retinal ciliopathy. The existence of this mostly unrecognized pattern of extramacular relative preservation in LCA5-LCA, as well as in other molecular forms of LCA, warrants further exploration.

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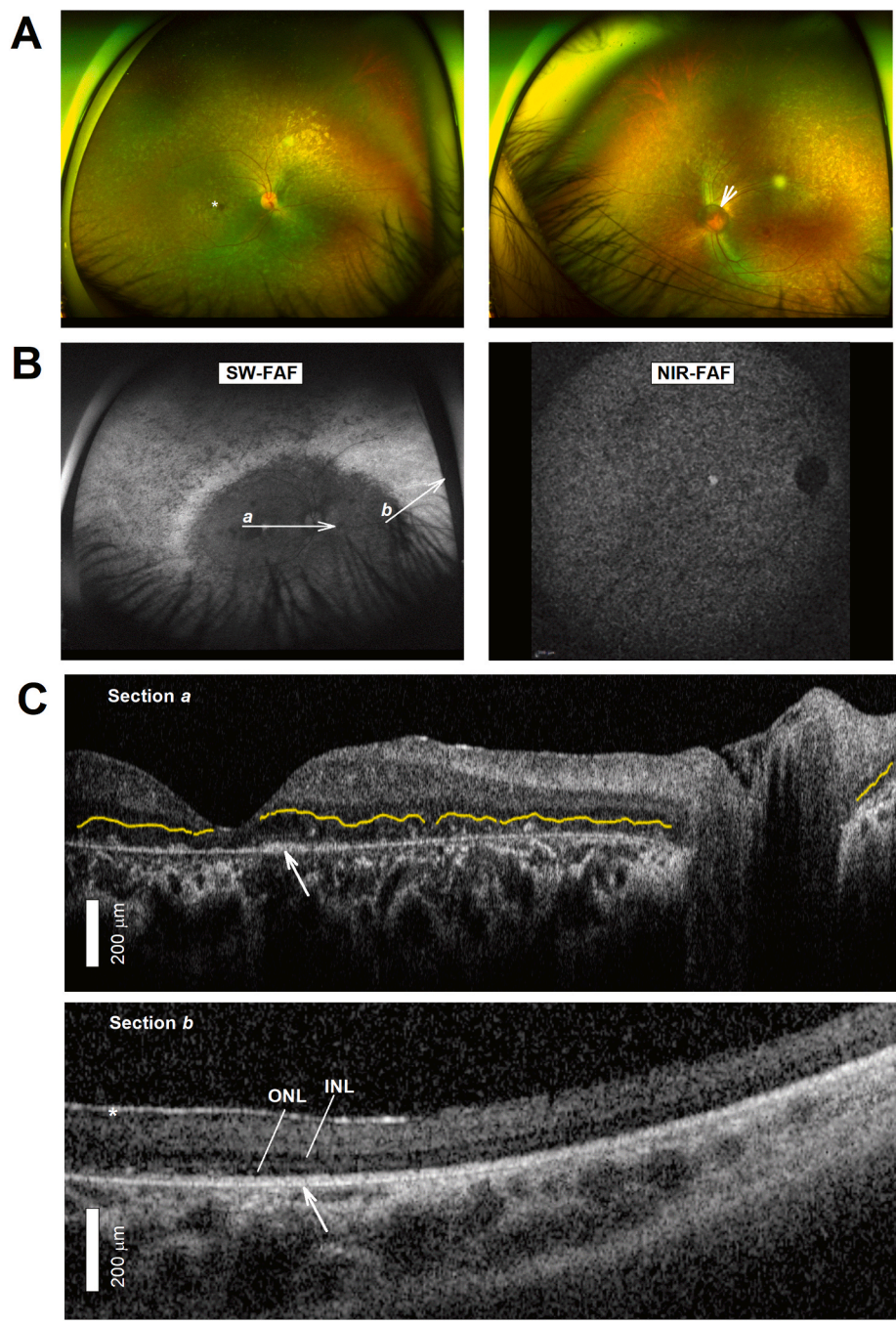


Fig. 1. A. Wide-field (Optos, Inc., Marlborough, MA) color fundus photography retinal imaging for the right (left panel) and left eye (right panel) of the patient. Asterisk is adjacent to a small island of preserved foveal RPE in the right eye; arrow points to outline of vitreous cyst anterior to the optic nerve in the left eye. B. Fundus autofluorescence short-wavelength (SW-FAF) and near-infrared (NIR-FAF) excitation lights in the right eye of the patient (Spectralis, Heidelberg Engineering, Carlsbad, CA). C. Non-straightened, 9 mm-long SD-OCT cross-sections along the horizontal meridian through the fovea (Section a) and in the nasal midperiphery (Section b); the location and direction of the scans are shown as overlaid arrows on the SW-FAF image (B). Outlined in yellow is the outer plexiform layer. Asterisk in section b denotes presence of epiretinal membrane. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Authorship

All authors attest that they meet the current ICMJE criteria for authorship. Informed consent was obtained; all procedures followed institutional guidelines of the University of Pennsylvania (protocol numbers 815348 and 832468), and complied with the Declaration of Helsinki.

Declaration of competing interest

No conflict of interest for any of the authors.

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