



Published in final edited form as:

Ophthalmic Genet. 2017 December ; 38(6): 575–579. doi:10.1080/13816810.2017.1323339.

Peripapillary sparing in *RDH12*-associated Leber congenital amaurosis

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Abstract

Background: Peripapillary sparing is a characteristic that is traditionally described as pathognomonic for Stargardt disease.

Materials and methods: We present a multi-modal assessment of four f Leber Congenital Amaurosis (LCA) cases with congenital macular atrophy and severely attenuated electroretinogram findings caused by bilallelic mutations in *RDH12*.

Results: Fundus autofluorescence imaging revealed a general loss of retinal pigment epithelium across the macula except for the peripapillary region in both eyes of all patients. Spectral domain-optical coherence tomography confirmed relative preservation in this area along with retinal thinning and excavation throughout the rest of the macula. LCA was diagnosed based on clinical exam and retinal imaging, and subsequently confirmed with genetic testing.

Conclusions: Peripapillary sparing is a novel phenotypic feature of *RDH12*-associated LCA.

Keywords

Autofluorescence; Leber congenital amaurosis; peripapillary sparing; *RDH12*; spectral domain optical coherence tomography

INTRODUCTION

Leber congenital amaurosis (LCA) refers to a clinically and genetically heterogeneous group of inherited retinal dystrophies characterized by a progressive, early-onset visual

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

impairment, nystagmus and amaurotic pupils.^{1,2} The cause of LCA is attributed to mutations in several genes that include *GUCY2D*, *RPE65*, *SPATA7*, *AIPL1*, *CEP290*, *RPGRIP1*, *NMNAT1*, and *RDH12*.^{3,4} The clinical spectrum of LCA comprises clinical features of other inherited retinal disease such as cone-rod dystrophy and retinitis pigmentosa. Peripapillary sparing is a finding considered pathognomonic of Stargardt disease (STGD1), a recessive, juvenile-onset maculopathy caused by mutations in the ATP Binding Cassette Subfamily A Member 4 (*ABCA4*). Visual symptoms in STGD1 begin in the second or third decade of life (Cideciyan et al., 2005) and can often progress to retina-wide degeneration due to the accumulation of toxic bisretinoid-containing lipofuscin in the retinal pigment epithelium (RPE). Although these are both devastating retinal dystrophies, they have distinct genetic etiologies. This report describes cases of four children with clinical and electrophysiologic manifestations of LCA caused by mutations in *RDH12*, whose fundus imaging and spectral domain-optical coherence tomography (SD-OCT) demonstrate a unique incidence of peripapillary sparing.

METHODS

Genetic analyses.

DNA isolated from whole blood lymphocytes was sequenced for candidate genes by the Casey Eye Institute Diagnostic Laboratory (Portland, Oregon). One patient (P3) underwent whole exome sequencing performed by the Columbia University Medical Center Pathology Department (New York, NY).

Electroretinography.

Full-field electroretinogram (ffERG) (Diagnosys LLC, Lowell, Massachusetts, USA) recordings were acquired in all patients from both eyes per International Society for Clinical Electrophysiology of Vision (ISCEV) standards in scotopic and photopic states. DTL recording electrodes were utilized for all patients.⁵

Imaging.

All imaging was performed as previously described by Sujirakul et al.⁶ After dilation, each patient underwent digital fundus photography and both fundus short-wavelength autofluorescence (SW-AF) and SD-OCT imaging using a Spectralis HRA+OCT device (Heidelberg Engineering, Heidelberg, Germany). For SW-AF imaging, 30-degree views were acquired at 1536 × 1536 pixel resolution using a 486nm wavelength stimulus and 521nm barrier filter. SD-OCT imaging was performed with an 870nm light source and automated real-time infrared reflectance image registration. Horizontal scans were positioned through the fovea (high resolution mode, 9mm window, ART, minimum of 50 averaged images). Microperimetry was performed using the Nidek MP-1 (Nidek Technologies; Padova, Italy).

FINDINGS

Cases 1 and 2

A 16-year-old boy (P1) was diagnosed with LCA13 presented with best-corrected visual acuity (BCVA) of 20/50 in the right eye and 20/100 in the left eye, equally reactive pupils, no relative afferent pupillary defect, and intraocular pressure of 14 mmHg in both eyes. Ophthalmoscopy revealed extensive macular atrophy, peripheral pigment migration, as well as peripapillary and para-arterial sparing.

SD-OCT demonstrated marked retinal thinning and excavation at the macula, with sparing of RPE atrophy in the peripapillary region of each eye (Fig. 1A, inset). SW-AF imaging (Heidelberg Spectralis HRA+ OCT version 1.7.0.0; Heidelberg Engineering, Heidelberg, Germany) revealed a pattern of hypoautofluorescence consistent with the loss of RPE throughout the macula with the exception of the peripapillary region of each eye (Fig. 1B).

ffERG revealed extinguished photopic and scotopic responses consistent with a generalized loss of cone and rod function, respectively. Microperimetry exhibited marked decreases in visual sensitivities over the fovea and a complete loss of visual function in the parafoveal region. Fixation was foveal in an area of low-decibel cone sensitivity (Supplemental Fig. 1). The peripapillary region was not sampled.

The patient's 21-year-old sister (P2) had an identical macular phenotype, with the additional finding of horizontal nystagmus (Fig 2, Fig 3). Direct sequencing of several candidate genes identified homozygous missense mutations p.L99I in exon 3, predicted to be deleterious by SIFT in both siblings. Microperimetry in this case showed foveal fixation with complete loss of visual function in the sampled area, which did not include the parapapillary area (Supplemental Fig. 1).

Case 3

An independent case of an 8-year-old girl (P3) has striking similarities with the siblings described above. The patient had BCVA of 20/60 in the right eye and 20/80 in left, with eccentric fixation, equally reactive pupils, no relative afferent pupillary defect, and normal intraocular pressures in both eyes. Ophthalmoscopy revealed dense intraretinal pigmentation in the macular and peripherally with peripapillary sparing. SD-OCT, FAF, and CFP findings were similar to the previously described cases. ffERG on this patient revealed extinguished photopic and scotopic responses indicating generalized retinal dysfunction affecting both rods and cones. Whole exome sequencing identified homozygous missense mutations (p.V233D) in the *RDH12* gene.

Case 4

A 10-year-old boy (P4) presented for evaluation after previously being diagnosed with retinitis pigmentosa at the age of 3-years-old. He complained of night blindness but had no history of nystagmus. Past medical history was unremarkable and no other family members were similarly affected. The patient had a BCVA of 20/30 in the right eye and 20/60 in the left. Dilated fundus exam revealed depigmentation atrophy of both maculae with bilateral

peripapillary sparing (Fig. 4D and 4E). The fundi showed extensive mottling but very little pigment migration. The far peripheral retina had a salt-and-pepper appearance. SD-OCT showed marked atrophy of the RPE (Fig. 4A), however, with intact retinal cell layers in the peripapillary regions (Fig. 4C), correlating to AF findings bilaterally (Fig. 4B). fERG showed extinguished rod responses and diminished 30 Hz-flicker responses of approximately 10 μ V in both eyes confirming a rod-cone dystrophy. Genetic testing was performed at Casey Eye Institute (Portland, Oregon), identifying a c.806_820delCCCTG and p.Arg295Stop:c.C>T mutation in the *RDH12* gene, for which each parent was a carrier of one allele, confirming the diagnosis of early onset retinal dystrophy.

DISCUSSION

These patients are, to our knowledge, the first reported case series of LCA with lack of RPE atrophy in the peripapillary region, a finding that is traditionally reserved for Stargardt disease (STGD1) in the context of retinal degenerations.^{7,8}

RDH12, an LCA candidate gene, maps to chromosome 14q23 (8Mb from the *LCA3* locus), and has been localized to photoreceptor inner segments.⁹ A missense or frameshift mutation in *RDH12* is associated with an autosomal recessive progressive retinal degeneration characterized by severe and progressive rod-cone dystrophy with severe macular atrophy that leads to visual loss before the second decade of life.¹ Structurally, an OCT in this condition typically reveals a distorted retinal architecture that can vary in thickness and prohibits identification of normal laminae.⁹ The L99I variant of *RDH12* found in P1 has been described to include reduced visual acuity and hyperpigmentation in the mid-periphery of the fundus.¹⁰ Our four *RDH12* cases demonstrate macular atrophy and hyperpigmentation similar to those reported in the literature, but also uniquely exhibit peripapillary and para-arterial sparing.

Peripapillary sparing in STGD1 has been attributed to this region's favorable photoreceptor-to-RPE ratio and thicker overlying retinal nerve fiber layer, creating a reduction in load of light on the photoreceptor-RPE complex, and, thus, less photo-oxidative damage.⁷ The role of *RDH12* in the visual cycle is well-characterized and dysfunction of this enzyme leads to decreased synthesis of 11-cis-retinal.¹¹ Reduced light stimulus near the peripapillary region may also theoretically temper the degenerative process as *RDH12* plays a key role in phototransduction. However, while these reasons may contribute to the observed phenotype, gene-specific features are likely responsible for our findings. Aside from its presence in STGD1, peripapillary sparing has been described in RDS/Peripherin 2 Pattern Dystrophy¹² and in one case report of pigmentary retinal dystrophy in which RPE mottling and pigment clumping spared the peripapillary and foveal regions.¹³ Interestingly, Cideciyan et al. provided a functional assessment of the peripapillary region in Stargardt disease.⁷ In patients with an eccentric focus, 30% had a preferred locus in the peripapillary retina, suggesting superior retinal function in this region. For P1 and P2 who underwent microperimetry testing, fixation was foveal and sensitivity was not measured in the peripapillary region. Future studies are needed to discern the retinal function in the peripapillary region of *RDH12*-associated LCA patients, and assess if these findings correlate to the structural observations we describe on multimodal imaging.

Concurrent incidence of STGD1 and LCA in our patients was considered clinically unlikely, as the patients' phenotype was typical of LCA. The ophthalmic exam revealed reduced perception of light, nystagmus, and pigmentary changes, which is consistent with previous descriptions of LCA.^{14,15} ERG findings corroborated clinical exams, demonstrating undetectable waveforms, which are consistent with the LCA phenotype.¹⁴ Such a finding would be considered highly unlikely in STGD1, in which only a fraction of the diseased population demonstrates any ERG changes. STGD1 ERG group I, which is characterized by a normal scotopic and photopic ERG, displays a trend toward relative functional and structural sparing in the peripapillary region. Those in STGD1 ERG groups II or III display altered ERG limited to macular involvement as well as peripapillary atrophy.⁸

The p.D2177N variant of *ABCA4* found in the siblings (P1 and P2) has been reported to occur in 8% of patients with age-related macular degeneration (AMD)^{16,17}; however, a subsequent study showed that the frequency of this variant was not statistically associated with an increased risk of developing AMD.¹⁸ This variant is predicted benign and unlikely to be a disease-causing allele for STGD1 ruling out any trans modifier effects. Although variations in *ABCA4* have been extensively associated with STGD1, no such phenotypic correlations have been ascribed to D2177N. In addition, mutations in *RDH12* have not been reported in the setting of STGD1.

Whole exome sequencing may allow us to detect specific variants responsible for the patients' phenotype; however, our findings prompt clinical awareness of shared manifestations in conditions with distinct genetic origins. This case demonstrates a novel presentation of LCA as a subphenotypic overlap of STGD1, and may be representative of a dual effect of *RDH12* and *ABCA4*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

Jonas Children's Vision Care, and Bernard & Shirlee Brown Glaucoma Laboratory are supported by the National Institutes of Health [5P30EY019007, R01EY018213, R01EY024698, R01EY026682, R21AG050437], National Cancer Institute Core [5P30CA013696], the Research to Prevent Blindness (RPB) Physician-Scientist Award, unrestricted funds from RPB, New York, NY, USA. J.D.S is supported by the RPB Medical Student Research Fellowship. S.H.T. is a member of the RD-CURE Consortium and is supported by the Tistou and Charlotte Kerstan Foundation, the Schneeweiss Stem Cell Fund, New York State [C029572], the Foundation Fighting Blindness New York Regional Research Center Grant [C-NY05-0705-0312], the Crowley Family Fund, and the Gebroe Family Foundation.

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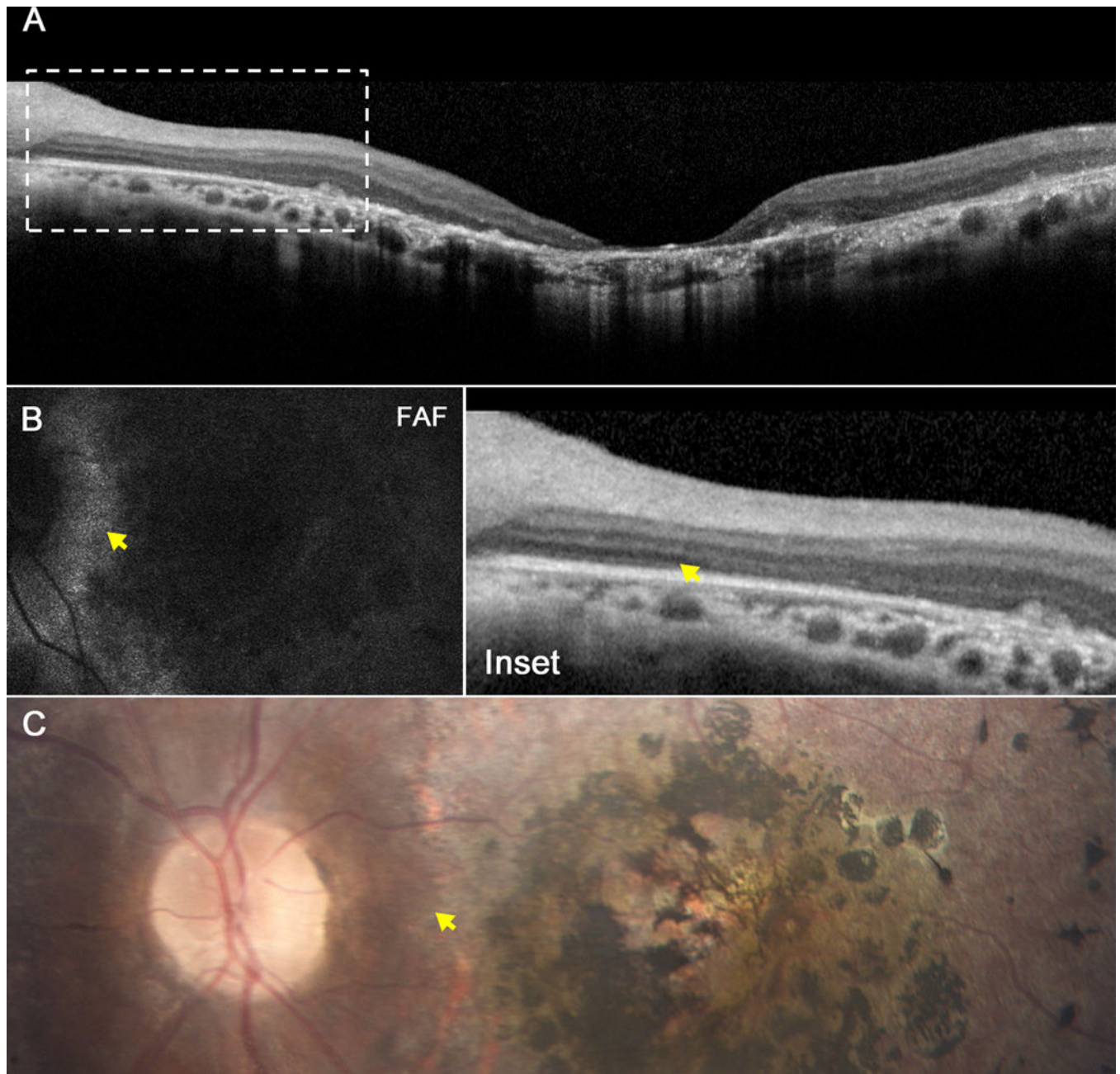


Figure 1.

Retinal images from the 16-year-old brother (P1). Spectral domain-optical coherence tomography (SD-OCT) reveals loss of photoreceptors and ellipsoid nuclei throughout the macula with exception of the peripapillary region (A), and magnification demonstrates preservation of the retinal pigment epithelium and inner segment ellipsoid band (inset). These findings correlate with fundus autofluorescence images (B), which reveal hypofluorescence throughout the macula except for in the peripapillary region, as well as color fundus photography (C), which demonstrates atrophy of the retinal pigment epithelium with a bone spicule-like pattern, with sparing of the peripapillary region. Yellow arrows in each image mark the edge of sparing and in SD-OCT, the loss of retinal architecture.

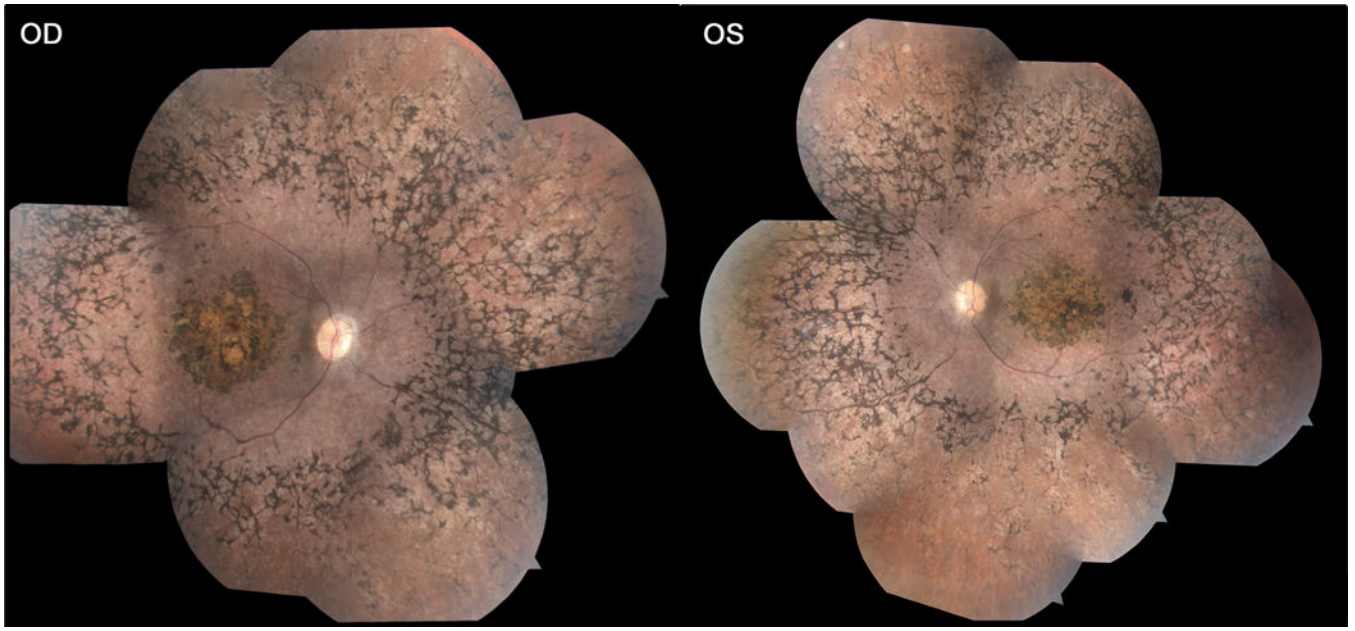


Figure 2. Color fundus photography of P2 reveals localized macular atrophy of the retinal pigment epithelium circumscribed by a confluent bone spicule pigment pattern in the beyond the vascular arcades in the periphery in both eyes.

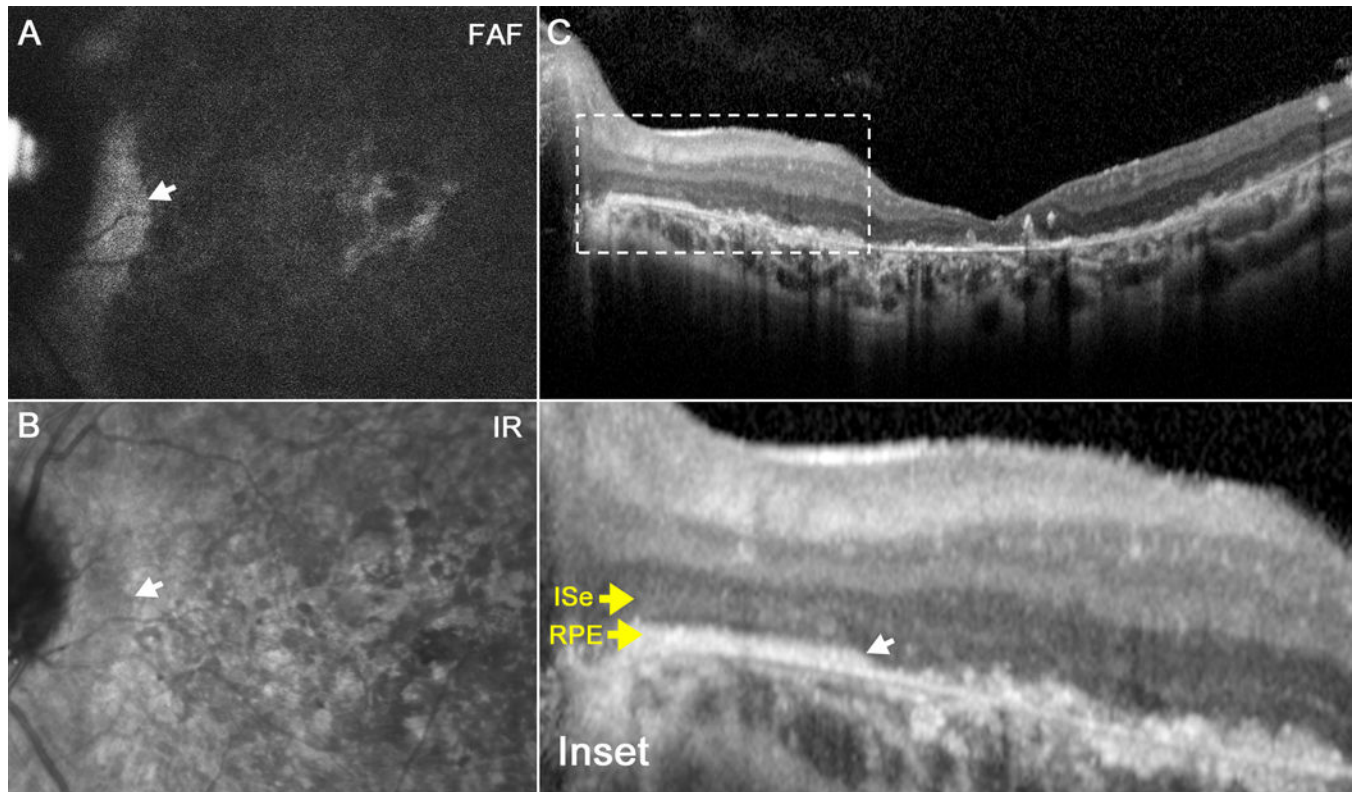


Figure 3. Scanning laser ophthalmoscopy images from the 21-year-old sister (P2). Fundus autofluorescence and infrared images reveal macula-wide hypoautofluorescence (a) and hyporeflectance (b), respectively, with peripapillary sparing in each eye. Spectral domain-optical coherence tomography reveals loss of photoreceptors and ellipsoid nuclei in a similar pattern (C). Magnification reveals intact retinal architecture limited to the peripapillary region (inset).

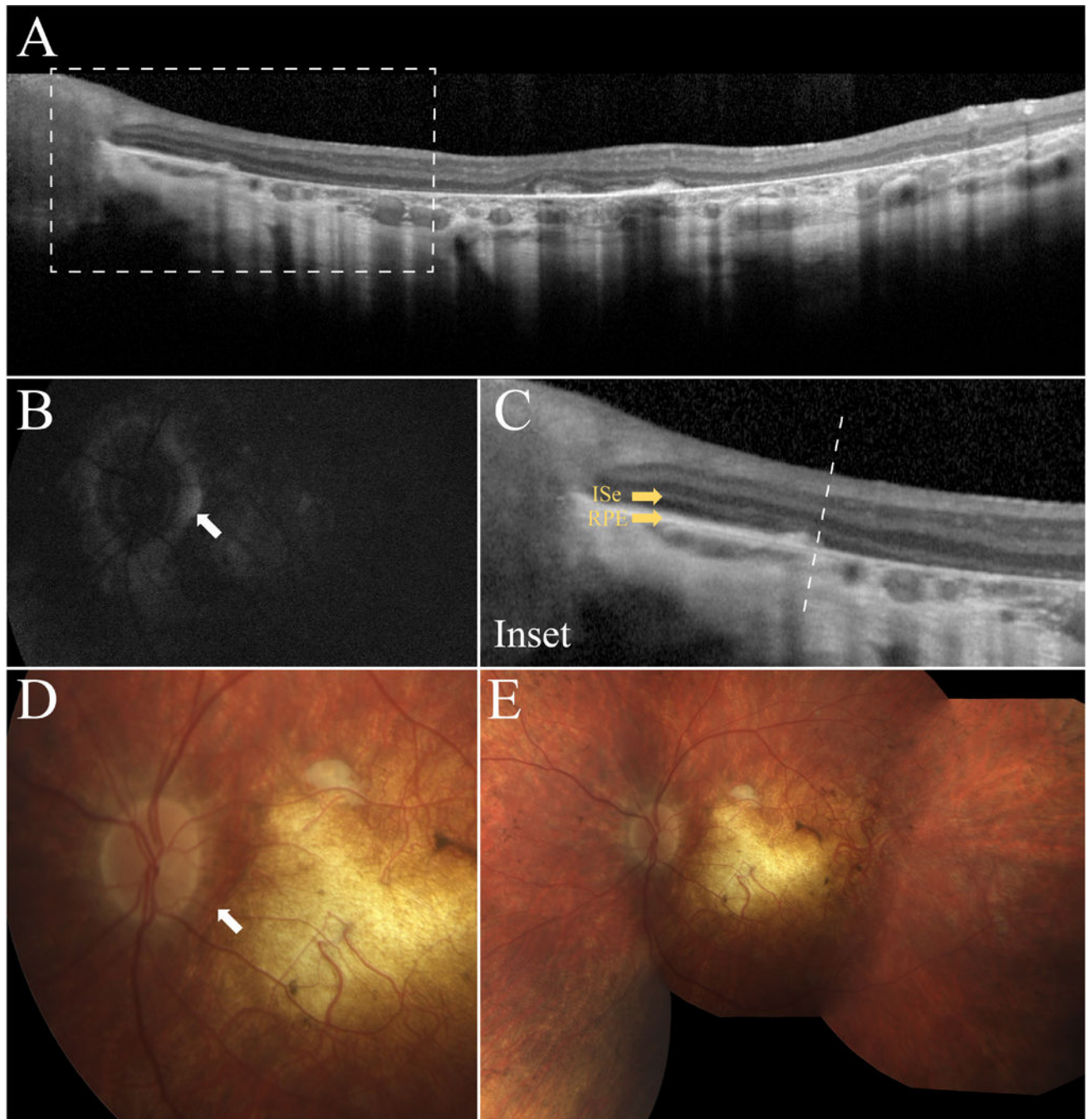


Figure 4. Retinal imaging of the 10-year old boy (P4). SD-OCT shows extensive RPE and photoreceptor atrophy in the macula (A) and relative preservation of the RPE and retinal structure in the peripapillary region (C). SW-AF (B) imaging and color fundus photography (D and E, respectively) corroborate SD-OCT findings and show ubiquitous hypofluorescence and hyporeflectance that is spared immediately surrounding the optic nerve.