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Case Report

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Phenotypic characterization of CRB1-associated Leber congenital amaurosis in two siblings: emphasis on para-arteriolar RPE preservation

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ABSTRACT

Leber congenital amaurosis (LCA) associated with CRB1 mutations exhibits a distinct retinal phenotype, most notably para-arteriolar retinal pigment epithelium preservation (PPRPE), an important yet often under-recognized diagnostic hallmark. We report two affected female siblings from a consanguineous family who underwent comprehensive multimodal ophthalmic evaluation, including best-corrected visual acuity assessment, color fundus photography, spectral-domain optical coherence tomography (OCT), fundus autofluorescence (FAF), and full-field electroretinography (ERG). Both demonstrated congenital severe visual impairment and nystagmus. Fundus examination revealed bilateral nummular pigmentation with characteristic PPRPE, while FAF showed para-arteriolar hyperautofluorescence consistent with preserved RPE integrity. OCT demonstrated diffuse retinal thinning, macular disorganization, and peripheral atrophy, and ERG responses were markedly reduced or extinguished. Next-generation sequencing identified a homozygous pathogenic CRB1 variant, c.2843G>A, p.(Cys948Tyr) (NM_201253), classified as pathogenic according to ACMG-2015 criteria, confirming CRB1-associated LCA. Additional affected male family members further supported autosomal recessive inheritance. The coexistence of PPRPE, macular structural abnormalities, and severe electrophysiological dysfunction aligns with the established CRB1 phenotypic spectrum. These findings reinforce the diagnostic utility of PPRPE in differentiating CRB1-associated LCA from other molecular subtypes and underscore the importance of integrating multimodal imaging with early molecular testing to facilitate accurate diagnosis, targeted genetic counseling, and potential future eligibility for emerging genotype-directed therapies.

Keywords: Leber congenital amaurosis, CRB1 gene, para-arteriolar retinal pigment epithelium, optical coherence tomography, fundus autofluorescence

INTRODUCTION

Leber congenital amaurosis (LCA) represents the most severe form of inherited retinal dystrophy presenting in early infancy and is genetically heterogeneous, with more than twenty genes implicated to date.[1] Among these, CRB1 is a well-established cause of LCA and early-onset severe retinal dystrophy (EOSRD), accounting for approximately 10% of cases in large cohorts.[2,3] Pathogenic variants in CRB1 disrupt the Crumbs complex, a critical regulator of photoreceptor polarity, retinal lamination, and Müller cell integrity.[4,5] As a result, CRB1-associated retinopathies exhibit a distinct constellation of structural abnormalities, including coarse retinal lamination, thickened retina in early disease stages, and progressive macular disorganization.[2,6]

One of the hallmark clinical features of CRB1-associated LCA is para-arteriolar retinal pigment epithelium preservation (PPRPE), a striking and highly characteristic fundus sign first recognized more than two decades ago.[7] PPRPE reflects selective preservation of RPE along retinal arterioles despite widespread peripheral atrophy and is increasingly recognized as a valuable diagnostic clue guiding early genotypic suspicion.[2,7,8] Recent studies highlight its utility in differentiating CRB1-associated LCA from other genetic subtypes such as CEP290 or RPE65, which lack this distinctive pattern.[9,10] However, despite its diagnostic value, PPRPE remains underreported and may be overlooked without multimodal imaging techniques such as fundus autofluorescence (FAF) and optical coherence tomography (OCT).[6,8]

Multimodal imaging plays a central role in the phenotyping of CRB1-associated retinopathies. FAF often demonstrates para-arteriolar hyper autofluorescence consistent with preserved RPE integrity, whereas OCT reveals inner retinal disorganization, altered retinal lamination, and progressive atrophy.[6,8,11] Full-field electroretinography (ERG) typically

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shows severely reduced or extinguished responses, reflecting widespread photoreceptor dysfunction.[12] The integration of these imaging modalities with next-generation sequencing (NGS) enables precise genotype–phenotype correlation and informs genetic counseling and emerging gene-based therapeutic strategies.[13,14]

Here, we present two affected female siblings from a consanguineous family with genetically confirmed CRB1-associated LCA. We emphasize the diagnostic relevance of PPRPE supported by multimodal imaging and highlight the clinical features, electrophysiological characteristics, and molecular findings that contribute to accurate diagnosis and improved understanding of the CRB1-LCA phenotype.

CASE

Two affected female siblings from a consanguineous family were referred to our inherited retinal disease clinic for evaluation of lifelong visual impairment. Both individuals exhibited symptoms consistent with congenital onset LCA, including poor visual behavior in infancy and early nystagmus. A detailed family history revealed additional affected male relatives on the paternal side, supporting an autosomal recessive inheritance pattern.

Patient 1

A 31-year-old female reported stable but severely reduced visual acuity since infancy. Best-corrected visual acuity (BCVA) was 20/200 in right eye and counting fingers at 1 meter in the left eye. Anterior segment examination was unremarkable. Fundus photography showed bilateral nummular pigmentary deposits, attenuated retinal vessels and prominent PPRPE (Figure 1). FAF, obtained using the Zeiss Visucam platform, demonstrated para-arteriolar hyperautofluorescence corresponding to preserved RPE integrity, surrounded by peripheral hypo autofluorescent atrophic zones (Figure 2). Both patients exhibited high hyperopia and normal intraocular pressures (14-15 mmHg).

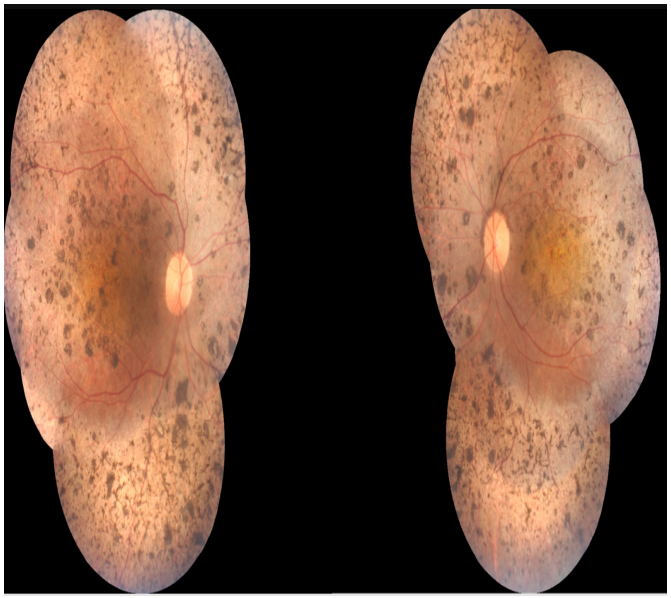

Figure 1. Color fundus photograph of the 31-year-old female sibling
Color fundus photography showing para-arteriolar RPE preservation (PPRPE), nummular pigmentation, vascular attenuation

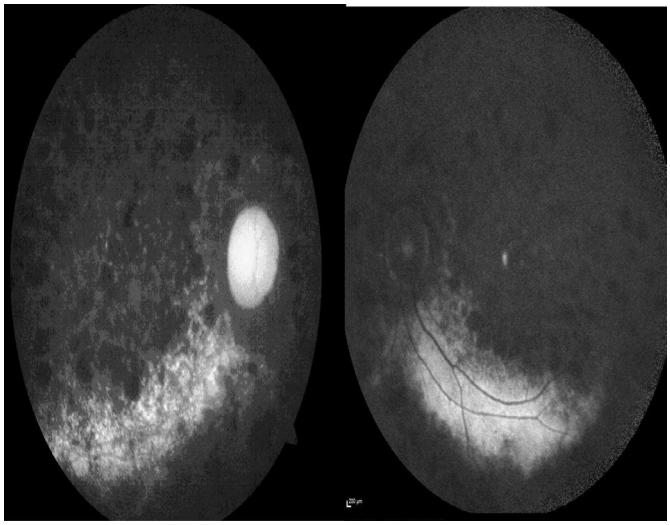

Figure 2. Fundus autofluorescence demonstrating para-arteriolar hyper autofluorescence with peripheral hypo autofluorescence

Spectral-domain optical coherence tomography (SD-OCT; Carl Zeiss Stratus OCT III) revealed diffuse retinal thinning, disruption of the outer retinal layers, and central macular disorganization with loss of the photoreceptor IS/OS junction (Figure 3). Full-field ERG; Metrovision Mon 2021A, ISCEV-standard showed extinguished scotopic and photopic responses, indicating severe global retinal dysfunction.[12]

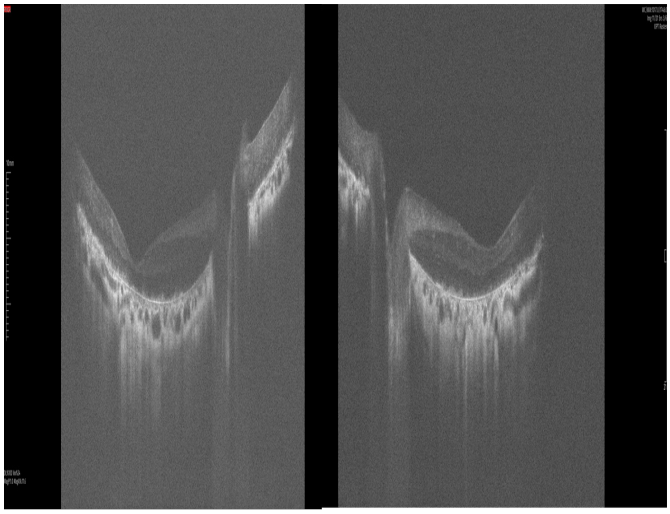

Figure 3. Spectral-domain optical coherence tomography (SD-OCT) of the elder sister
OCT demonstrating Diffuse retinal thinning, foveal contour distortion, and loss of outer retinal layers.

Patient 2

A 19-year-old female sibling reported similar congenital visual impairment. BCVA measured 20/400 bilaterally. The younger sibling demonstrated horizontal nystagmus, while ocular motility and anterior segment examination were otherwise unremarkable. Fundus examination demonstrated a nearly identical phenotype, including bilateral PPRPE, nummular pigmentation, vascular attenuation, and optic disc drusen (Figure 4). FAF imaging showed para-arteriolar hyper autofluorescence with more pronounced central hypo autofluorescence compared with her sister (Figure 2). SD-OCT demonstrated advanced retinal thinning, laminar disorganization, and perifoveal atrophy (Figure 5). ERG responses were extinguished across all modalities.

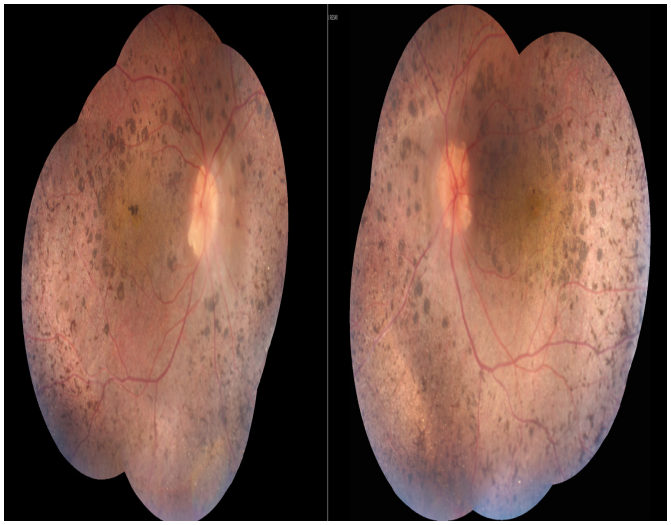

Figure 4. Colour fundus photograph of the 19-year-old female sibling
Color fundus photography showing para-arteriolar RPE preservation (PPRPE), nummular pigmentation, vascular attenuation and optic disc drusen

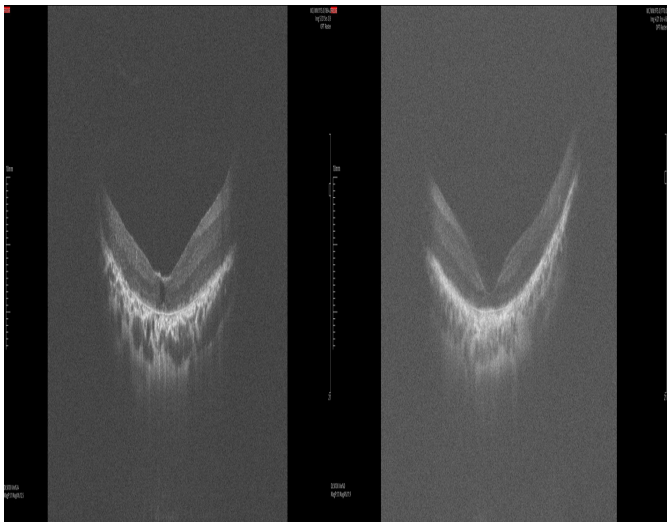

Figure 5. Spectral-domain optical coherence tomography (SD-OCT) of the younger sister
OCT demonstrating more advanced thinning, laminar disorganization, and perifoveal atrophy

Genetic Findings

Both siblings underwent targeted NGS using a 41+ gene inherited retinal disease (IRD) panel on the Illumina sequencing platform. Sequencing reads were aligned to the GRCh37/hg19 reference genome. The assay achieved mean coverage >100× and >99% of coding regions covered at ≥20×, meeting standards for IRD molecular diagnostics.[3,13]

NGS revealed a homozygous c.2843G>A, p.(Cys948Tyr) pathogenic variant in CRB1 (NM_201253), classified as pathogenic according to ACMG-2015 criteria. The variant is previously reported in association with CRB1-LCA and demonstrated high pathogenicity on in-silico analysis (CADD, PolyPhen-2, MutationTaster). Genetic findings confirmed CRB1-associated LCA in both siblings.

Based on clinical, electrophysiological and genetic findings, a diagnosis of CRB1-related LCA was made. Both patients were referred for low-vision rehabilitation and supportive educational services. They were also counseled regarding potential participation in emerging gene therapy clinical trials for CRB1-associated retinal dystrophies. (A detailed summary of clinical imaging and genetic findings is provided in Table.)

DISCUSSION

LCA associated with CRB1 mutations represents a distinct clinical and structural phenotype within the spectrum of early-onset inherited retinal dystrophies. The two affected siblings presented here demonstrate several hallmark features of CRB1-associated disease, including congenital severe visual impairment, extinguished electroretinographic responses, PPRPE, and characteristic multimodal imaging abnormalities. Their findings closely parallel the phenotypic patterns reported in large CRB1 cohorts.[2,6,8]

PPRPE has long been recognized as a distinctive hallmark of CRB1-related retinopathies.[7] Mechanistically, several hypotheses have been proposed. First, para-arteriolar regions

Table. Clinical, imaging, and genetic characteristics of the two affected siblings

Parameter	Sibling 1 (age 31)	Sibling 2 (age 19)
Sex	**Female**	**Female**
Family history	Consanguineous parents; additional affected males	Consanguineous parents; additional affected males
Onset	Congenital	Congenital
BCVA (Snellen)	20/200 OD 20/400 OS	20/400 OU
Anterior segment	Normal	Horizontal nistagmus
Fundus findings	Nummular pigmentation; vessel attenuation; PPRPE	Nummular pigmentation; vessel attenuation; PPRPE; optic disc drusen; more pronounced pigmentary changes
FAF	Para-arteriolar hyper autofluorescence with peripheral hypo-AF	Identical pattern; more central hypo-AF
SD-OCT	Diffuse thinning; macular disorganization; outer retinal loss	Severe thinning; laminar disorganization; perifoveal atrophy
ERG	Severely reduced/extinguished	Extinguished
VEP	Delayed latency, reduced amplitude	Delayed latency, reduced amplitude
Genetic testing	Homozygous CRB1 c.2843G>A, p.(Cys948Tyr)	Homozygous CRB1 c.2843G>A, p.(Cys948Tyr)
NGS panel coverage	Mean depth >100×; >99% bases ≥20×	Mean depth >100×; >99% bases ≥20×
Final diagnosis	CRB1-associated LCA	CRB1-associated LCA

BCVA: Best-corrected visual acuity, FAF: Fundus autofluorescence, SD-OCT: Spectral-domain optical coherence tomography, ERG: Electroretinography, PPRPE: Para-arteriolar retinal pigment epithelium preservation, LCA: Leber congenital amaurosis, VEP: Visual evoked potential, NGS: Next-generation sequencing

may exhibit relative RPE and Müller cell resilience, supported by differential metabolic demand or structural support along arterioles.[5] Second, oxygen tension may be comparatively higher adjacent to retinal arterioles, preserving RPE viability in these zones despite widespread degeneration.[15] Third, CRB1—a critical component of the Crumbs complex—helps maintain retinal epithelial polarity and adherens junctions, and its dysfunction may lead to selective RPE vulnerability except in areas with compensatory Müller cell support.[4] These mechanistic models collectively explain why PPRPE remains one of the most reliable clinical markers of CRB1 involvement.

The value of PPRPE is further underscored when differentiating CRB1-LCA from other genotypes. In contrast to CRB1 disease, RPE65-associated LCA typically exhibits widespread early RPE dysfunction without para-arteriolar sparing.[10] Likewise, CEP290-LCA often demonstrates severe foveal hypoplasia and preserved retinal architecture in infancy but does not show PPRPE.[9] Thus, PPRPE represents an important diagnostic clue, enabling clinicians to prioritize CRB1 analysis early in the diagnostic pathway.

The prognostic significance of PPRPE remains a subject of ongoing study. While some authors have suggested that areas of preserved RPE may correlate with localized structural stability,[6,7] current evidence does not support a clear association between the presence of PPRPE and slower global disease progression. Phenotypic severity among CRB1 patients is highly variable—even in individuals carrying the same variant.[2,8] Our two siblings, both exhibiting PPRPE, nevertheless demonstrated advanced structural and functional deterioration, reinforcing that PPRPE should be regarded primarily as a diagnostic, rather than prognostic, feature.

Genotype–phenotype relationships in CRB1-associated disease are similarly complex. Studies suggest that loss-of-function variants often produce more severe phenotypes with early retinal disorganization,[2,4] whereas missense variants, including the p.(Cys948Tyr) substitution identified in our patients, may result in a broader clinical spectrum with some retention of para-arteriolar RPE integrity.[8,11] The variant detected in this family has been previously reported and is consistently classified as pathogenic. The shared homozygous genotype in both siblings, combined with multiple affected family members, supports autosomal recessive inheritance consistent with prior CRB1 reports.

Multimodal imaging serves as an indispensable tool for characterizing CRB1-associated LCA. FAF remains particularly sensitive in visualizing PPRPE, and SD-OCT reveals essential structural correlates, including inner retinal disorganization, thickened retinal layers in early stages, and progressive thinning with age.[8,16] ERG findings in our patients—severely reduced or extinguished responses—align with the advanced disease stage expected in adult CRB1-LCA.[12] The combination of multimodal imaging and NGS has become the cornerstone of accurate diagnosis and genotype–phenotype correlation in LCA, aligning with current consensus recommendations.[13]

As emerging gene-based therapies continue to expand for inherited retinal dystrophies, accurate molecular diagnosis of CRB1-associated disease is increasingly important. Although no approved CRB1-targeted therapy exists, several preclinical programs—including AAV-based gene augmentation and CRISPR-mediated editing—are in development.[14] Identifying affected families with confirmed pathogenic variants is therefore essential for future clinical trial eligibility.

CONCLUSION

This study describes two affected female siblings with genetically confirmed CRB1-associated LCA, demonstrating the classic phenotypic triad of PPRPE, macular structural abnormalities, and severe electrophysiological dysfunction. The findings reinforce the utility of multimodal imaging for early clinical suspicion and highlight the importance of integrating molecular diagnostics for accurate genotypic confirmation. PPRPE remains a key distinguishing feature of CRB1-associated disease, although its prognostic significance is limited. As gene-based therapeutic strategies for CRB1-associated retinal dystrophies advance, early and precise diagnosis will become increasingly critical for counseling, family screening, and treatment eligibility.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patients included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

This case report did not receive any financial support.

Author Contributions

Concept: HZI; Design: HZI; Control: HZI, MYT; Resources: HZI, TZG, MYT; Materials: HZI, TZG; Data Collection and/or Processing: HZI, TZG; Analysis and/or Interpretation: HZI, MYT; Literature Review: HZI, TZG; Writing the Article: HZI, TZG, MYT; Critical Review: HZI, TZG, MYT.

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