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RESEARCH ARTICLE

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Bilateral Foveoschisis Due to a Mutation in CRB1: Clinical, Genetic and Multimodal Characterisation in a Case Report

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ABSTRACT

Purpose: To detail the clinical, multimodal imaging and genetic findings of a patient with bilateral foveoschisis caused by the in-frame c.498_506del (p.Ile167_Gly169del) variant in CRB1, emphasizing distinctions from other hereditary cystic maculopathies.

Case Description: A 19-year-old man presented with blurred vision (BCVA 20/40 OD, 20/50 OS). Anterior segment and peripheral retina were unremarkable. High-resolution macular OCT disclosed multilamellar intraretinal cavities and hyper-reflective "pillar" columns centred on the fovea; fundus autofluorescence showed a faint parafoveal hyper-autofluorescent halo without vitelliform or fleck deposits. Full-field ERG was normal (b/a ≈ 1.6); Goldmann perimetry and color vision were intact. A 330-gene retinal dystrophy panel identified the heterozygous in-frame deletion c.498_506del in CRB1 and excluded variants in RS1, BEST1 and ABCA4. A localized CRB1-associated cystic maculopathy was diagnosed; semi-annual monitoring and genetic counseling were instituted.

Conclusions: Hypomorphic CRB1 variants can produce isolated foveoschisis with preserved peripheral function and a normal ERG, clinically mimicking X-linked juvenile retinoschisis. High-resolution OCT combined with molecular confirmation is essential for accurate differential diagnosis, prognostication and potential enrolment in future CRB1 gene-based therapies.

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Introduction

The CRB1 gene (Crumbs homolog 1), mapped at 1q31.3, encodes a transmembrane protein that localizes to Müller cells and photoreceptor inner segments (IS), where it integrates the apical Crumbs-PALS1-PATJ-MPP5 complex and maintains the polarity and intercellular adhesion of the developing retina [1,2]. Bi-allelic mutations in CRB1 alter this architecture, causing disorganization of the outer limiting membrane (ELM) and progressive photoreceptor degeneration (PR) [3]. Variants affecting domains like epidermal growth factor "EGF-like" or laminin G of the extracellular portion compromise the stability of the junctions and favor the formation of cystic cavities or intraretinal retinoschisis [4].

The phenotypic spectrum of CRB1 retinopathies is broad. At the most severe end is Leber congenital amaurosis type 8 (ACL-8), characterized by blindness or minimal early visual acuity (VA), starting in the first months of life, and flat ERG [5]. Less severe forms include early-onset autosomal recessive retinitis pigmentosa (RP) and infantile cone-rod dystrophies [6]. Paravascular pigmentary chorioretinal atrophy (PPCRA) and RP with Coats-type vasculopathy have also been described [7]. Hypomorphic variants, missense mutations that retain residual activity, are associated with localized phenotypes, with good visual acuity, including chronic cystic maculopathy and familial foveal retinoschisis (FFR) [8].

Vincent et al. identified for the first time bi-allelic mutations in CRB1 responsible for FFR, possibly the most benign form of the clinical continuum [9]. The patients, mostly females, present with a mild decrease in visual acuity since childhood, foveal intraretinal cysts and normal peripheral retina. OCT reveals retinoschisis or foveal cystic edema with preserved extrafoveal integrity, which evolves in three phases: (a) pure foveal retinoschisis, (b) chronic cystic degeneration and (c) central macular atrophy in adulthood [9].

This phenotype can be confused with X-linked juvenile retinoschisis (XLRS), typical of males with RS1 mutations. Unlike XLRS, CRB1 retinoschisis: (a) presents autosomal recessive

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inheritance and affects both genders; (b) lacks the classic electronegative ERG; and (c) shows relatively preserved peripheral function [10]. Genetic analysis is, therefore, decisive to differentiate both entities and provide counseling.

Finally, from the point of view of clinical and therapeutic implications, recognizing a maculopathy linked to CRB1 mutations is important because of the possible association with other complications and the limited treatment options available. Although there is still no approved gene therapy for CRB1 dystrophies, the understanding of their molecular mechanisms has stimulated the development of experimental models and therapeutic strategies under investigation [10]. In the meantime, palliative measures are employed: carbonic anhydrase inhibitors can transiently reduce foveal thickness in CRB1-associated cystic maculopathies [11]. Accurate genetic diagnosis makes it possible to identify candidates for future testing and to estimate the risk of familial recurrence.

This is why CRB1 dystrophies range from fulminant ACL to localized maculopathies; the latter, such as bilateral foveal retinoschisis, constitute a diagnostic challenge and should be considered in the differential of hereditary cystic maculopathies. To illustrate the phenotypic heterogeneity of CRB1 mutations, highlighting the multimodal analysis and targeted genetic study, we present in detail a case of bilateral foveal retinoschisis attributable to a pathogenic biallelic variant in this gene.

Clinical Case

Male patient, 19 years old, university student and athlete, with no medical history, medication use, family history or parental consanguinity.

He initially consulted in 2022 due to blurred vision of approximately three months of evolution that makes it difficult to read the blackboard or see the projector, associated with photophobia and glare sensation in front of intense lights.

At the time of consultation, best corrected visual acuity (BCVA) of 0.5p in the right eye (OD) with -0.50 cil 175° and 0.4 with -0.50 cil 135° in the left eye (OS), ocular tonometry 12 mmHg in both eyes. Biomicroscopy (BMC) of the anterior segment without pathological findings. Fundus both eyes (AU): bilateral polycystic maculopathy, with areas of peripheral retinoschisis, papillae of normal appearance, without other lesions.

Complementary study, when analyzing the macular optical coherence tomography (OCT) showed complete foveal retinoschisis, symmetrical in both eyes (Figures 1 and 2).

30° infrared slice (left panel) with green scan line and 9 mm B-scan section (right panel). Foveal retinoschisis is seen with intraretinal cavities converging on the fovea with subfoveal disruption of the ellipsoid area, and the characteristic hyperreflective columns extending from the inner plexiform layer (IPL) to the outer limiting layer (ELM). The perifoveal retina maintains its laminar architecture with mild schisis.

30° infrared image with scan path (left panel) and 9 mm B-scan slice (right panel). Symmetric foveal schisis with hyperreflective columns delimiting multilamellar intraretinal cavities is identified. Disruption of the ellipsoid band is observed in the subfoveal area; the perifoveal retina preserves its architecture.

With these findings, X-linked juvenile macular retinoschisis was suspected, so the study was complemented with electrophysiology (ERG FF / MF) (Figure 3), autofluorescence (FAF), visual field (CVG) and color vision tests were normal, in

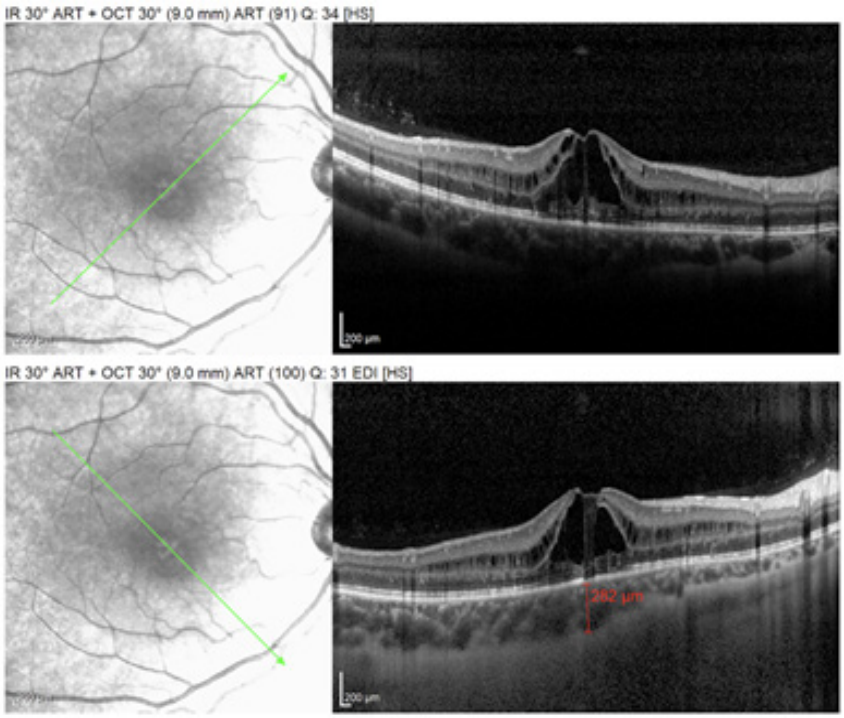


Figure 1: Macular OCT of the right eye (OD).

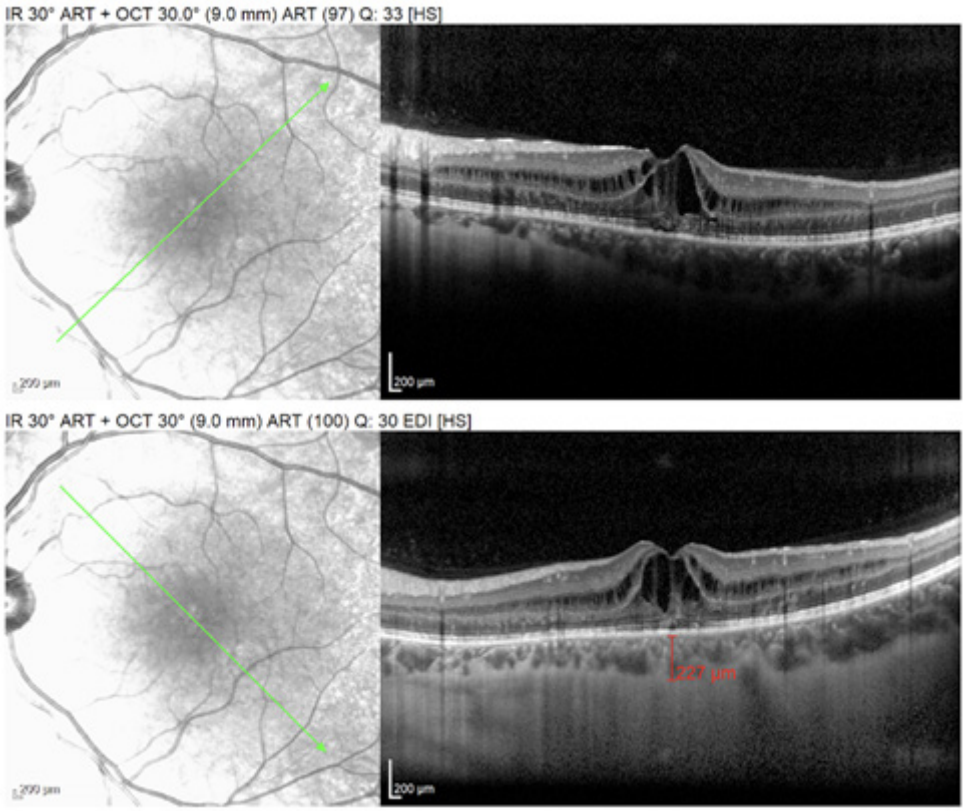


Figure 2: Macular OCT of the left eye (OS).

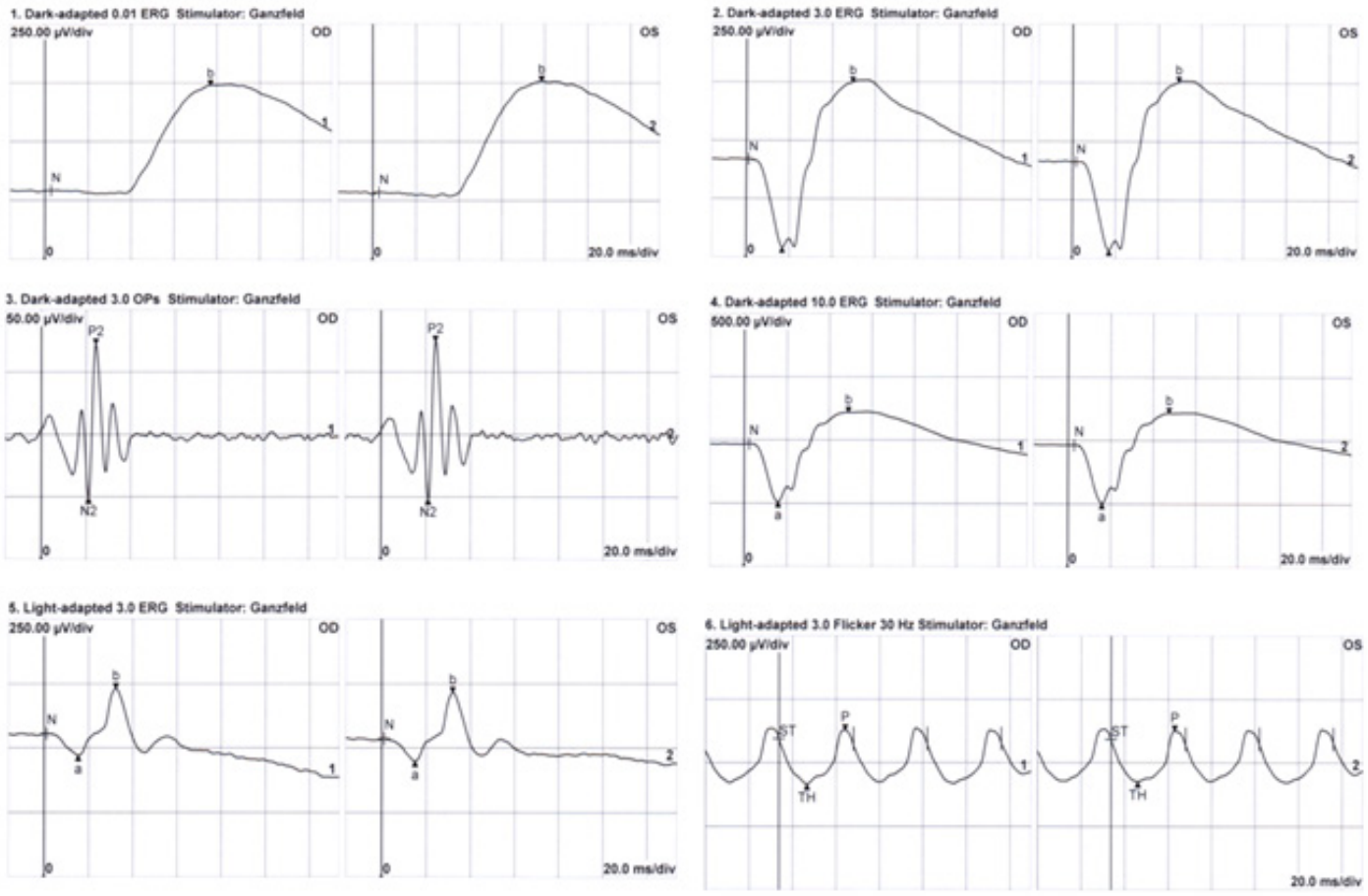
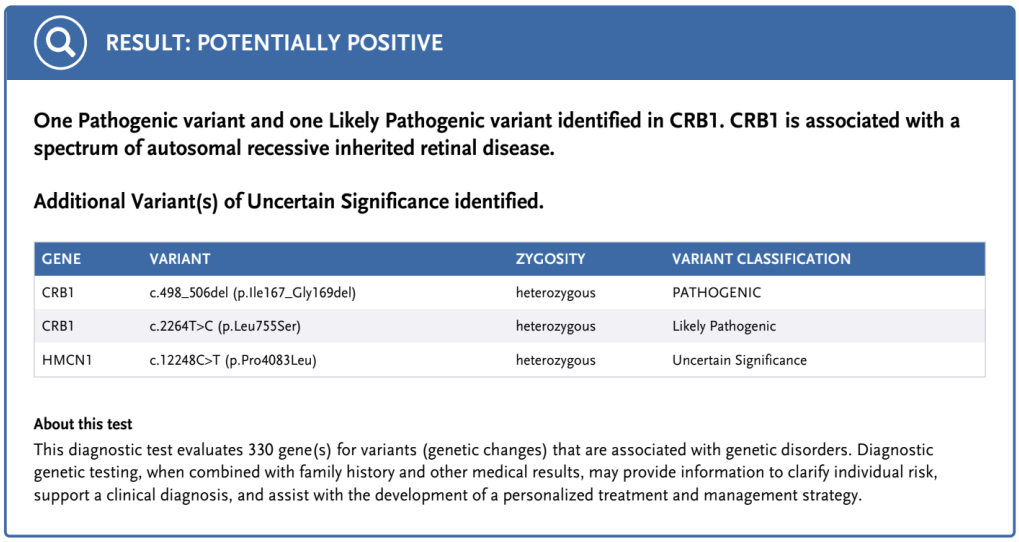


Figure 3: Ganzfeld electroretinogram, both eyes (AU).



RESULT: POTENTIALLY POSITIVE

One Pathogenic variant and one Likely Pathogenic variant identified in CRB1. CRB1 is associated with a spectrum of autosomal recessive inherited retinal disease.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
CRB1	c.498_506del (p.Ile167_Gly169del)	heterozygous	PATHOGENIC
CRB1	c.2264T>C (p.Leu755Ser)	heterozygous	Likely Pathogenic
HMCN1	c.12248C>T (p.Pro4083Leu)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 330 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Figure 4: Retinal dystrophy panel sequencing report.

addition to referral to ocular genetics for further study.

Binocular recording, according to ISCEV protocols [15]. Scotopic 0.01 cd-s/m²: rod response; b-waves present. Scotopic 3.0 and 10.0 cd-s/s/m²: mixed maxima; a- and b-waves preserved morphology, with b/a ratio ≈ 1.6, no electronegative pattern. Photopic 3.0 cd-s/m² and flicker 30 Hz: cone-dependent responses present (b-wave ≈ 268 µV OD, 268 µV OS; stable flicker), evidencing relatively preserved peripheral function.

Functional study based on multimodal analysis evidenced, normal color vision test, normal visual fields and normal full field ERG; however, regarding the genetic analysis, the study revealed mutation in the CRB1 gene variant c.498_506del (p.Ile167_Gly169del) in heterozygous exon 2 (Figure 4), which confirmed the diagnosis of CRB1-associated cystic maculopathy.

A periodic follow-up plan, genetic counseling and surveillance for possible complications (e.g. angular closure or "Coats" type vasculopathy) was established without specific treatment for the time being.

Discussion

Retinal dystrophies secondary to bi-allelic mutations in CRB1 were initially described in the context of Leber's congenital amaurosis (LCA) and early-onset retinitis pigmentosa (RP), which are generalized and devastating for vision; However, molecular characterization of larger cohorts revealed that certain hypomorphic alleles, especially in-frame deletions and missense variants, can cause a localized macular phenotype with bilateral foveal retinoschisis as a hallmark [11,12].

Our case shows this benign spectrum, whose reason for consultation in adolescence was a moderate decrease in visual acuity (VA), and in the multimodal analysis presents cystic spaces located in the fovea in the OCT, preserved peripheral retina and a practically normal full-field ERG [13].

This clinical presentation of findings differs from the classic presentation of diffuse CRB1 disease, where generalized chorioretinal atrophy and flat electroretinogram (ERG) are observed [14,15]. In the genetic analysis of 330 genes, a heterozygous in-frame mutation was identified in the CRB1 gene (c.498_506del). This is a relevant finding, as it has recently been associated with localized macular dysfunction, often manifesting foveal schisis with normal peripheral retina, as described in the literature [16].

From the clinical-diagnostic point of view, the entity most frequently confused with foveal retinoschisis due to CRB1 is X-linked juvenile retinoschisis (XLRS). Both share the presence of cystic cavities in the macula and an onset in childhood-adolescence; however, there are subtle but crucial differences. XLRS almost exclusively affects hemizygous males with RS1 mutations and presents, in most cases, with a characteristic electronegative ERG, severely reduced b-wave with relatively preserved a-wave and, not infrequently, inferotemporal peripheral schisis [17]. In our patient, the ERG showed normal "a" and "b" wave amplitudes and no peripheral schisis was identified and no variants in RS1 were detected, which led to search for alternative etiologies.

Another relevant differential diagnosis is Best's vitelliform dystrophy. The juvenile form may present with sub foveal hyperreflectivity and macular thickening, but is usually accompanied by markedly increased autofluorescence, whose clinical manifestation at the foveal level has a "fried egg" appearance and a functionally pathognomonic abnormal electrooculogram (EOG); none of these were present in our case. Likewise, in Stargardt's disease, which presents with mutations in ABCA4, OCT may show cystic cavities in early stages, although the presence of hyper-reflective pisciform flecks on autofluorescence (AF) and the finding of a dark choroid on angiography usually facilitate differentiation [18]. Finally, entities such as Goldmann-Favre syndrome with NR2E3 mutations combine retinoschisis with rod-cone involvement and a disorganized ERG, features absent in this observation [19].

Table 1: Differential diagnosis CRB1-associated foveoschisis and X-linked Retinoschisis.

Finding	CRB1-foveal	XLRS (RS1)	Best (BEST1)	Stargardt (ABCA4)
Sex / pattern	Both sexes, AR	Males, X	AD, both sexes	Both sexes, RA
Age at onset	5-20 a	5-15 a	5-20 a	10-25 a
OCT	Pure foveal schisis with hyperreflective "columns"; normal periphery.	Foveal schisis + peripheral schisis ± "cartwheel".	Subfoveal vitelliform detachment.	Foveal thinning, hyperreflective deposits sub-EPR
ERG FF	Normal or mild b-wave; b/a ≈1.6	Electronegative (b ↓, a≈N)	Normal	Early normal, ↓ cone/late normal.
FAF	Normal or subtle halo	Normal	Hyper-AF vitelliform	Flecks hyper/hypo-AF + "dark choroid".
Color	Normal	Normal slightly affected	Early normal	Early red-green defect
Genetics	Hypomorphic CRB1 mutation	RS1 mutation	BEST1 mutation	ABCA4 mutations

CVG = Goldmann visual field**, ERG FF =** full-field electroretinogram**, FAF =** autofluorescence**, OCT =** optical coherence tomography**, AR =** autosomal recessive inheritance**, AD =** autosomal dominant inheritance**, XLRS =** X-linked retinoschisis**, XLRS =** X-linked retinoschisis.

Autofluorescence (AF) and high-resolution OCT were mandatory to rule out these alternatives and support the suspicion of a CRB1-linked structural maculopathy. The discretely annular hyperautofluorescent AF pattern around the fovea, without flecks or vitelliform deposits, is consistent with previous descriptions of CRB1 retinoschisis [6,7]. The hyperreflective columns extending from the inner plexiform layer (IPL) to the external limiting membrane (ELM), present in our patient and referred to as "pillars" in the literature, have been related to altered Müller cell-photoreceptor junctions secondary to partial loss of function of CRB1-A [8,9].

The genetic finding of the deletion c.498_506del (p.Ile167_Gly169del), reported in several patients with focal macular dystrophy, provides a molecular explanation clinically concordant with the case. Genotype-phenotype correlation studies demonstrate that this in-frame variant preserves the CRB1-B isoform expressed in photoreceptors, while compromising the CRB1-A isoform of Müller cells, resulting in separation of inner layers without early loss of peripheral PRs [12,14]. In comparison, nonsense variants or frameshifts, by abolishing both isoforms, are associated with LCA or retinitis pigmentosa of fulminant course.

Recognition of this mild phenotype has therapeutic and prognostic implications. First, it allows to guide genetic counseling, with a recurrence risk of 25% for siblings and absence of sex-linked transmission [17]. Second, it justifies a follow-up focused on macular progression and the eventual development of Coats-like vasculopathy or central atrophy, complications described although infrequent in hypomorphic variants [9-11]. For now, there is no approved gene therapy for CRB1, but detailed knowledge of the mutation opens the door to trials based on dual AAV vectors or variant-specific gene editing. In the meantime, the use of carbonic anhydrase inhibitors, topical dorzolamide and brinzolamide [5,8], is a therapeutic option; however, modest reductions in foveal thickness and visual stability have been documented in prolonged follow-up, with no clear long-term benefit [5]. In our patient, expectant management was considered, with surveillance by VA and serial OCT. Table 1 summarizes the differential diagnoses to be considered.

In summary, bilateral foveal retinoschisis due to CRB1 should be suspected in an adolescent or young adult, with exclusively macular schisis, normal wide-field ERG and absence of vitelliform deposits or flecks. Genetic confirmation is crucial to differentiate it from XLRS and other maculopathies, as well as to predict its relatively benign course. Advances in the understanding of the different CRB1 isoforms and their interactions with Müller cells and photoreceptors are redefining the therapeutic approach, with the expectation that gene therapy strategies for these localized phenotypes will emerge in the coming years, offering patients the possibility of preserving their central vision beyond the second decade of life.

Conclusion

This case report corresponds to a bilateral symmetrical foveoschisis associated with mutations in the *CRB1* gene. Among the distinctive features, there is no peripheral involvement or severe alterations in the ERG. The identification of the heterozygous in-frame mutation c.498_506del in CRB1 reinforces the growing evidence that certain hypomorphic variants can generate localized and milder phenotypes, such as familial foveal retinoschisis, moving away from the classic spectrum of severe dystrophies associated with this gene. Genetic analysis is key in these cases, not only for an accurate diagnosis, but also to differentiate entities with similar phenotypes, such as X-linked retinoschisis, and to properly guide follow-up, management and genetic counseling. Despite the absence of curative treatments, early recognition of this presentation allows close monitoring and timely symptomatic management, in a condition that usually evolves slowly towards central macular atrophy with initial foveolar preservation.

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