Case Report

ISSN 2639-9482

Ophthalmology Research

A Novel Variant in CRB1 Associated with Paravenous Chorioretinal Atrophy and Dyschromatopsia

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Received: 15 Feb 2023; **Accepted:** 28 Mar 2024; **Published:** 06 Apr 2024

Citation: Ariza-Torrado Irina P, Martínez-Córdoba Claudia J, Hosse-Ovando Valeria, et al. A Novel Variant in CRB1 Associated with Paravenous Chorioretinal Atrophy and Dyschromatopsia. Ophthalmol Res. 2025; 8(2); 1-3.

ABSTRACT

Purpose: *To report a novel pathological variant of CRB1 previously reported in pigmented paravenous chorioretinal atrophy (PPCRA), present in an infant with color-vision abnormalities.*

Case Report: *A 6-year-old male is brought for consultation by his parents for noticing color vision deficiency. Visual acuity was 20/30 (LogMAR 0.2) and 20/20 (LogMAR 0.0) in the right and left eye, respectively. Ophthalmologic examination was unremarkable, and optical coherence tomography and retinography were normal. Farnsworth-Munsell test was initially normal but follow-up test at 6-months was altered in protanope, deuteranomal and tritanope. Genetic testing revealed a pathogenic variant in CRB1: c.2506 A (p.Pro836Thr).*

Conclusion: *CRB1 mutations have been associated with a spectrum of ocular diseases, including retinitis pigmentosa, Leber's congenital amaurosis, and early-onset angle-closure glaucoma. A pathogenic variant associated with PPCRA was found, a rare disorder with no-specific treatment. Most PPCRA patients maintain a stable vision, though the case here presented was associated with dyschromatopsia.*

Keywords

CRB1 mutation, Dyschromatopsia, Pigmented paravenous chorioretinal atrophy.

Introduction

Crumbs homolog 1 (CRB1) is a large extracellular and transmembrane protein, expressed in the retinal pigment epithelium and in the brain. The CRB1 gene is mapped to chromosome 1q31.3 [1]. CRB1 is expressed in the inner and outer segments of the photoreceptors and in Muller glial cells, where its function is to maintain cell adhesion epithelial and photoreceptor morphogenesis and apico-basal polarity during retinal development [1,2]. CRB1 mutations affect organization during retinal development interrupting the naturally occurring process of apoptosis, leading to multiple phenotypes of retinal dystrophies [2]. Autosomal recessive mutations are associated with Leber congenital amaurosis and retinitis pigmentosa, whereas autosomal dominant mutations are associated with pigmented paravenous chorioretinal atrophy [3], however, cases of primary angle-closure glaucoma associated with CRB1 mutations have also been reported [4].

Leber congenital amaurosis is a severe and early onset retinal dystrophy [5], described by Theodore Leber in 1869 as a severe visual impairment in infants, accompanied by nystagmus and poor pupillary light reflex [6]. Common causal mutations include GUCY2D, CRB1, RPE65, CEP290, RDH12 [7,8], of which CRB1 accounts for 13.6% of cases [9]. Typical clinical findings include progressive macular atrophy with nummular pigmentation and preserved para-arteriolar retinal pigmented epithelium (RPE) [10].

Retinitis pigmentosa (RP) is an inherited retinal disease, degenerative and progressive, that leads to profound vision loss

[11]. Its characterized by night blindness, followed by progressive loss of peripheral vision, that in many cases culminates in complete blindness [12]. Typical findings include bone spicule pigmentary deposits, attenuation of retinal vessels and electroretinogram changes. RP has genetic heterogeneity (different genetic mutations cause the same disease phenotype), allelic heterogeneity (many different disease-causing mutations in each gene), phenotypic heterogeneity (different mutations in the same gene cause different diseases) and clinical heterogeneity (same mutation produce different clinical signs). Fifty-six genes causing non-syndromatic RP have been described [12].

Pigmented paravenous chorioretinal atrophy (PPCRA) is a rare bilateral condition characterized by retinal pigment epithelium degeneration, coriocapillaris atrophy and pigmentation along retinal veins [13], it is more common in males, mean age at diagnosis is 36 years, and the majority of cases are diagnosed as an incidental finding in asymptomatic patients, though some symptoms include photopsias, blurred vision, peripheral visual fields loss and nyctalopia [14]. Two characteristic fundoscopic appearances have been identified: paravenous choroidal atrophic changes with pigment migration, and paravenous choroidal atrophic changes without pigmentary disturbances. No alterations can be found in optical coherence tomography and only areas of reduced signal corresponding to areas of retinal pigmentation are seem in fluoresceine angiography. Electroretinogram can evidence generalized retinal dysfunction [13]. Therefore, diagnosis is based on clinical fundoscopic examination and can be confirmed through electrophysiology [14]. The disease may have a genetic, inflammatory or infectious etiology, and has been associated with sarcoidosis, syphilis, tuberculosis, among other entities. Only one case of a heterozygous CRB1 mutation of dominantly inherited PPCRA has been reported [15].

A heterozygous CRB1 variant has also been associated with an early onset closed angle glaucoma case reported in a 15-yearl-old female, who presented with elevated intraocular pressure (IOP) and iris plateau. As retinal findings, attenuation of retinal vessels and cystoid macular edema were present, interpreted as a case of RP without the typical pigmentary changes [16]. We present the case of an infant that was brought to ophthalmology consultation for alterations in color vision, and in whom a mutation in CRB1 was found as positive. Informed consent was obtained from parents and assent was obtained from patient prior to the publication of this case.

Case Report

A 6-year-old male child is brought for consultation by his parents, who had noticed color vision deficiency. Best corrected visual acuity was 20/30 (LogMAR 0.2) in the right eye (OD) and 20/20 (LogMAR 0.0) in the left eye (OS). External slit-lamp examination was unremarkable, and IOP was 14mmHg in OD and 13mmHg in OS. Vitreous was clear and both fundi appeared normal. Farnsworth-Musell test was taken on the first consultation with a normal result, and subsequent assessments were indicated every 6 months for follow-up. Patient returns 6 months later, with a Farnsworth-Munsell test altered in protanope, deuteranomal and tritanope (Figure 1). With these findings, macular and optic nerve Optical Coherence Tomography (OCT) were obtained, with a normal result (Figure 2). Interconsultation with genetics and retina services were requested.

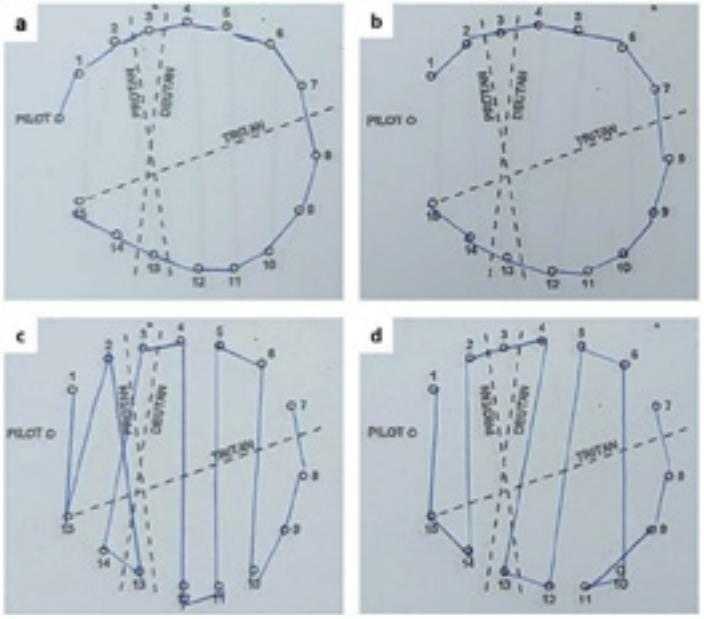

Figure 1: Farnsworth-Munsell color vision test comparing results at baseline for right eye (a) and left eye (b), and results at 6-month follow up for right eye (c) and left eye (d).

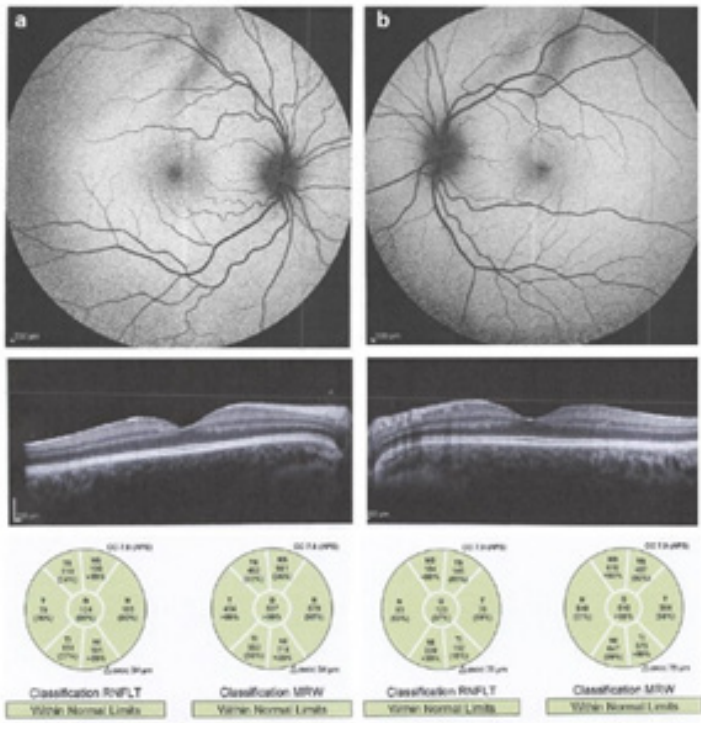

Figure 2: Macular Optic Coherence Tomography (OCT) displaying fundus image, macular cube and Retinal Nerve Fiber Layer Thickness (RNFLT) and Minimum Rim Width (MRW) values, which appeared normal for both right eye (a) and left eye (b).

Retina service did not find any anatomical alterations in the posterior segment and, in addition to OCT, retinography was performed, again with a normal result. Genetics service assessed the patient and his parents in order to obtain more information on similar cases in the family and background information and proceeded with genetic testing, revealing that a pathogenic variant was identified in CRB1: c.2506 A (p.Pro836Thr), which has previously been reported in PPCRA.

Discussion

This patient presented a pathogenic variant in CRB1 which is associated with PPCRA, a rare disorder of ill-elucidated etiology for which no-specific treatment exists. There is not enough literature that describes the course of this disease, but overall, most patients with PPCRA maintain a stable vision, and it is considered a non-progressive or slowly-progressive disease [13]. The patient here reported, was found to have a good visual acuity, showing only color-vision alterations, evidenced through Farnsworth-Musell test. To the extent of our knowledge, this is the first reported case of dyschromatopsia associated to a CRB1 mutation. For the meantime, only clinical follow-up is indicated for this finding [1,13].

CRB1 mutations have been associated with multiple ocular diseases, such as RP, PPCRA, and Leber's congenital amaurosis, there is even one reported case of a CRB1 mutation associated with early-onset angle closure glaucoma in a teenager [16], thus, the present case supports the conclusion that complete ophthalmological examination must be carried in all patients, even the younger ones, including IOP, gonioscopy and fundoscopic assessment.

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