• Letter to the Editor •

A novel *CRB1* variant presenting as Leber congenital amaurosis-8 with angle-closure glaucoma in a Chinese family

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Received: 2025-04-21 Accepted: 2025-06-11

DOI:10.18240/ijo.2026.03.25

Citation: Chen G, Wang ZR, Zhao C, Chen HH, Shi JM. A novel *CRB1* variant presenting as Leber congenital amaurosis-8 with angle-closure glaucoma in a Chinese family. *Int J Ophthalmol* 2026;19(3):630-633

Dear Editor,

We reported a Chinese family carrying a novel Crumbs homologue 1 (*CRB1*) variant (c.1737_1755del). Consanguineous marriage resulted in a homozygous mutation, leading to the onset of Leber congenital amaurosis (LCA) in their offspring. LCA is a rare inherited retinal dystrophy (IRD) causing severe visual impairment at early age, accompanied by nystagmus, and sluggish or absent pupillary responses. With a worldwide prevalence of 1/81 000 to 1/30 000 of newborn babies, it accounts for ≥5% of all IRDs[1-3]. Mutations in a variety of genes can potentially lead to the onset of LCA, with at least 21 mutated genes and over 400 mutations identified to date. Among them, *CEP290* (15%), *GUCY2D* (12%), and *CRB1* (10%) are the most frequently mutated LCA genes[4-6]. Due to the extensive genotypic diversity, the clinical phenotypes in individuals carrying LCA mutations exhibit significant heterogeneity. Overall, 18 distinct forms of LCA have been identified. Specifically, LCA type 8 (LCA8) results from mutations in the *CRB1* gene. In this case, we reported the clinical course and genetic mutation of a family with LCA8. This study was approved by the Ethics Committee of the Second Xiangya Hospital (No.20250122). Written informed consent was obtained from the patients.

CASE REPORT

The proband is a 45-year-old male patient, who has had poor vision in both eyes since childhood and presented to the Ophthalmology Department of the Second Xiangya Hospital due to sudden onset of distension and pain in the right eye, accompanied by a sharp decline in vision. His best-corrected visual acuity was no light perception (NLP) in right eye (OD) and light perception (LP) in left eye (OS), which is tested by penlight. Goldmann applanation tonometry values were 45 and 12 mm Hg in the right and left eyes, respectively. Slit-lamp examination of the anterior segment revealed bilateral microcornea, nystagmus, with mild corneal edema and significant mixed congestion in the right eye. The right anterior chamber was extremely shallow with complete angle closure. This was also confirmed by the ultrasound biomicroscopy (UBM; Quantal Medical, AVISO, France) in Figure 1A. The right pupil was fixed and dilated, showing no light reflex. The axial length measured 20.13 mm OD and 19.67 mm OS, and the anterior chamber depths were 0.3 and 1.6 mm in the right and left eyes, respectively. Fundus examination with 90 D preplaced lens showed that the right optic disc appeared pale with a cup-to-disc ratio of 1.0, while the left optic disc exhibited a ratio of 0.6. Fundus color photography demonstrated attenuated retinal vessels with extensive nummular pigment deposition and pigmentary disturbances (Figure 1B). Optical coherence tomography (OCT; Optovue, RTVue XR, USA) demonstrated bilateral macular coloboma. DNA was extracted from whole blood, and genetic testing was performed using panel-based targeted next-generation sequencing and whole exome sequencing. Sanger sequencing was performed to validate the variants from candidate genes. The transcript used to identify the variant in the *CRB1* gene was NM_201253. It revealed a homozygous *CRB1* variant, c.1737_1755del; p.L580Pfs*35 (Figure 2B). According to the American College of Medical Genetics and Genomics (ACMG) guidelines, we classify the c.1737_1755del; p.L580Pfs*35 mutation as pathogenic (PVS1+PM3+PM2_Supporting).

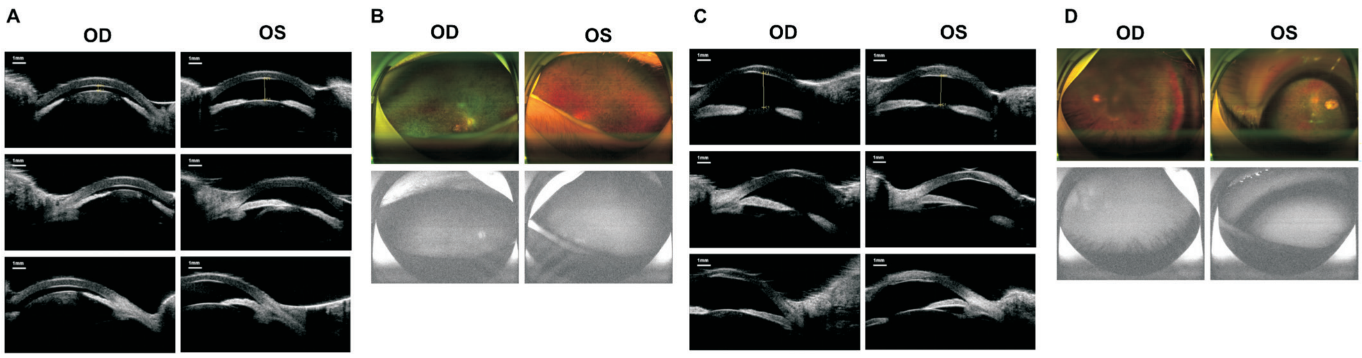

Figure 1 UBM, SLO and FAF images of the proband and his brother A: UBM image of the proband showed an extremely shallow anterior chamber (0.3 mm) and closed angle in the right eye during an acute angle-closure glaucoma attack. The left eye also exhibits a shallow anterior chamber (1.6 mm) and a narrow angle. Scale bars, 1 mm. B: SLO results of the proband showed attenuated retinal vessels, extensive nummular pigmentation, and macular defects. C, D: UBM, SLO and FAF results of the proband's brother showed similar characteristics. UBM: Ultrasound biomicroscopy; SLO: Scanning laser ophthalmoscopy; FAF: Fundus autofluorescence; OD: Right eye; OS: Left eye.

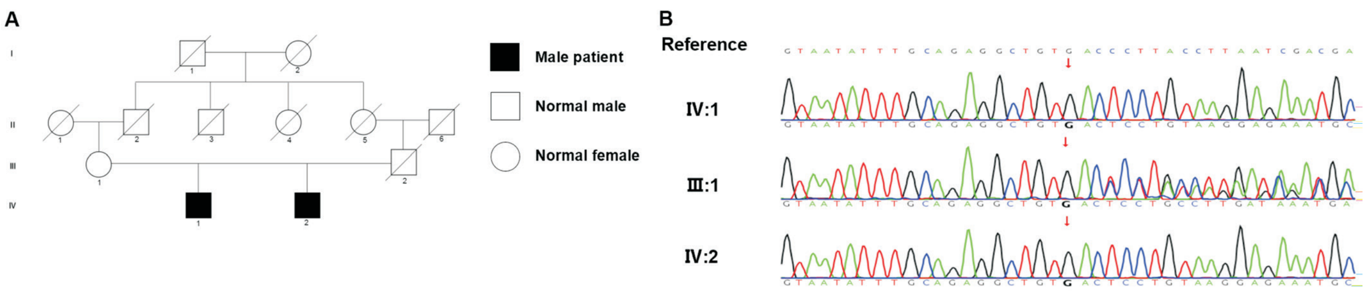

Figure 2 Family pedigree and *CRB1* gene mutation A: Family chart; B: Validation diagram of *CRB1* mutant generation.

In our study, the proband's eye examinations and genetic tests were consistent with the diagnosis of LCA8 complicated by acute angle-closure glaucoma. Given its severity and the age of onset, we did not categorize it as retinitis pigmentosa (RP). His brother, a 39-year-old male, also exhibited similar clinical manifestations (Figure 1C, 1D), and genetic testing revealed the same homozygous *CRB1* mutation. His parents are cousins, and both are heterozygous carrier of the mutant *CRB1* gene and exhibits no clinical symptoms. The pedigree is presented in Figure 2A.

In order to control the acute angle-closure glaucoma of the proband, we performed phacoemulsification (PHACO), goniosynechialysis, and trabeculotomy in the right eye to control the sharply elevated intraocular pressure (IOP). Following corneal incision, phacoemulsification with aspiration of the lens was performed. Gonioscopy-assisted angle separation was then conducted, followed by a 120° trabeculotomy (Shi JM). A preventive laser peripheral iridotomy (LPI) was administered to the left eye. After the surgery, the right eye was treated with standard postoperative medications to control inflammation for 1mo, including pilocarpine, prednisolone acetate and moxifloxacin. At the 2-week postoperative follow-up, IOP was well-controlled in both eyes.

DISCUSSION

In humans, the *CRB1* gene is situated on the long arm of chromosome 1 (1q31.1). This gene is responsible for encoding a transmembrane protein composed of 1406 amino acids, which resides in the subapical zone of the photoreceptor cells[7]. Mutations in *CRB1* cause multiple ophthalmic phenotypes, including LCA8, early onset rod cone dystrophy (EORCD), RP and cone-rod dystrophy (CRD). The typical characteristics of LCA include early and severe vision loss accompanied by nystagmus, photophobia, sluggish or absent pupillary responses, and behaviors such as pressing fingers on the eyeballs (Franceschetti sign). Fundus manifestations can range from normal, macular pathology, to typical RP-like abnormalities. Electroretinogram (ERG) may be undetectable or severely abnormal[4]. In fact, there is a significant clinical overlap between LCA and RP, making the diagnosis ambiguous in some cases. Bone spicule pigmentation, attenuation of retinal vessels, and a waxy pallor of the optic nerve—are the hallmark signs of RP[8]. Compared to LCA, early-onset RP is generally considered a relatively mild form, in which patients do not have congenital visual impairment. Most often, patients who present at birth or within the first few months of life are classified as having LCA. In our case, the proband's presentation of visual loss at birth, nystagmus, nummular pigmentation in the fundus, macular defects, and amaurotic pupils is consistent with the manifestations of LCA. His younger brother exhibits even more severe clinical symptoms. Indeed, *CRB1* mutation associated LCA8 has been documented in numerous cases. Sylla *et al*[9] has reported a novel CRB1 variant, c.3057 T>A; p.Tyr1019Ter in a 14-year-old male, who presented as LCA8. Duan *et al*[10] explored the variant (c.1499 C>G) in the *CRB1* gene in a Chinese family with LCA. However, to date, no one has documented the mutation variant of c.1737_1755del in *CRB1* gene, thus we are the first to report this variant.

The association between glaucoma and CRB1 LCA or RP was previously described by Talib *et al*[11] in a long-term follow-up study. They found that in 55 patients with *CRB1* mutation, 14% (7/55) presented with glaucoma. Notably, primary angle-closure glaucoma (PACG) accounted for 71% of these glaucoma cases. However, they did not investigate the specific pathogenesis of PACG in their patients. The *CRB1* gene can participate in promoting the axial growths of the head and eye during development. Thus, High hyperopia and nanophthalmos are frequently observed in patients with *CRB1* mutations. In our case, the proband presented with acute angle-closure glaucoma. We observed a decreased axial length and shallow anterior chamber that consistent with nanophthalmos. Therefore, we hypothesize that the acute angle-closure glaucoma is more likely secondary to a small eye size. In another case, the proband with the reported homozygous mutation c.1841G>T in *CRB1* was diagnosed with PACG, RP and nanophthalmos, which exhibits striking similarity to our case[12]. Two additional studies conducted on families harboring *CRB1* mutations also confirmed the correlation with nanophthalmos[13-14]. In fact, glaucoma induced by *CRB1* mutations is not merely secondary to microphthalmia. Abe *et al*[15] described a case of a patient with *CRB1* gene mutation experienced early occurrence of PACG induced by plateau iris syndrome. This indicates that the development of glaucoma associated with *CRB1* gene mutations may involve diverse underlying mechanisms.

We have administered effective interventions to manage the proband's acute angle-closure glaucoma. LPI was performed on the left eye, while the right eye underwent PHACO, goniosynechialysis, and trabeculotomy. The elevated IOP has been effectively controlled. However, the management of LCA8 remains challenging due to the lack of effective therapeutic options for patients with *CRB1*-mediated IRDs. Gene augmentation therapy is currently being employed as a therapeutic approach for a wide range of genetic diseases. The first ophthalmological disease to become the focus of gene therapy was indeed LCA, caused by disease-associated variants in retinal pigment epithelium-specific 65 kDa (RPE65)[16]. Voretigen neparvovec (Luxturna®, Novartis, Switzerland), the adeno-associated virus (AAV) designed to be administered to the sub-retinal space, was officially approved by the Food and Drug Administration (FDA) in the US in 2017 for the treatment of LCA caused by RPE65 variants. We hypothesize that a similar therapeutic approach may be applicable for *CRB1* mutations. However, the large size of CRB1, occupying nearly the entire packaging capacity of AAV, has made the development of a genetic therapy for these retinopathies challenging. Novel approaches through AAV vectors with small promoters have allowed the expression of *CRB1* protein in Müller glial cells *in vitro*. Commencement of trials is anticipated[17]. Furthermore, suprachoroidal delivery may serve as a new AAV administration strategy. It can be done in an outpatient setting and is less invasive and potentially safer than subretinal injection[18]. Researchers have found that suprachoroidal AAV injection enables widespread transgene expression while subretinal injection leads to focal gene expression[19]. Moreover, suprachoroidal AAV elicits less humoral immune reactivity to the viral capsid than intravitreal delivery. Therefore, suprachoroidal deliveries produce a more homogenous delivery of transgenes, avoiding risks of invasive surgery, and less systemic escape and humoral immunity[20]. In order to control nystagmus in LCA, more repeated cycles of biofeedback are recommended. It has been proposed that if patients can hear their own eye movements, they can use the feedback to control the nystagmus.

In this study, we report a novel variant c.1737_1755del of the *CRB1* gene occurred in a Chinese family with LCA, which broadening the spectrum of *CRB1* variants implicated in the etiology of LCA. This advancement not only facilitates a more profound comprehension of the pathogenic mechanisms of LCA, but also reveal new therapeutic targets. Furthermore, our case implies a potential link between *CRB1* mutations and the onset of glaucoma, offering fresh insights for the diagnosis of intricate ocular diseases.

ACKNOWLEDGEMENTS

Authors' Contributions: Shi JM and Chen HH contributed to the study conception and design. Material preparation, data collection and analysis were performed by Chen G, Wang ZR and Zhao C. The first draft of the manuscript was written by Chen G, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Artificial Intelligence Disclosure Statement: During the preparation of this work, the authors used DeepSeek in order to improve language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Foundations: Supported by the National Natural Science Foundation of China (No.81970804); Natural Science Foundation of Hunan Province (No.2021JJ30949).

Conflicts of Interest: Chen G, None; **Wang ZR,** None; **Zhao C,** None; **Chen HH,** None; **Shi JM,** None.

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