A novel nonsense variant (c.1499C>G) in CRB1 caused Leber congenital amaurosis-8 in a Chinese family and a literature review

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Abstract

Background: Leber’s congenital amaurosis (LCA) is a severe hereditary retinopathy disease that is characterized by early and severe reduction of vision, nystagmus, and sluggish or absent pupillary responses. To date, the pathogenesis of LCA remains unclear, and the majority of cases are caused by autosomal recessive inheritance. In this study, we explored the variant in the Crumbs homologue 1 (CRB1) gene in a Chinese family with LCA.

Methods: We conducted comprehensive ocular examinations and collected 5 ml of blood samples from members of a Chinese family with LCA. A pathogenic variant was identified by capturing (the panel in NGS) and Sanger sequencing validation.

Results: A nonsense variant (c.1499C>G) in the 6th exon of CRB1 gene in a Chinese family with LCA was identified, which predicted a change in the protein p. S500*, may lead to loss of gene function. We summarized the 76 variants reported thus far in CRB1 that caused LCA8.

Conclusions: This study reported a novel variant c.1499C>G (p. S500*) of the CRB1 gene occurred in a Chinese family with LCA, thus expanding the spectrum of CRB1 variants causing LCA.

Keywords: Leber’s congenital amaurosis, Variant, Crumbs homologue 1 (CRB1)

Introduction

Since Theodore Leber first described Leber’s congenital amaurosis (LCA) in 1869, a great deal of information about LCA has been revealed, including both clinical characteristics and molecular genetics. LCA, a rare but important juvenile retinal dystrophy, is an inherited retinal disorder most often diagnosed in infancy in the first 6 months of life and characterized by the presence of nystagmus, poor visual acuity (VA), and a severely reduced or nondetectable electroretinogram [1, 2]. The global incidence of LCA ranges from 1/81,000 to 1/30,000 among newborn babies. Although the incidence is low, this disorder also causes blindness in 20% of LCA school-age children and accounts for approximately 5% of all cases of hereditary retinopathy [3, 4]. LCA is currently categorized into 21 types according to the pathogenic genes, with autosomal recessive inheritance as the dominant. LCA8 is caused by a homozygous or compound heterozygous variant in the CRB1 gene (OMIM *604210) on chromosome 1q31.

Material and methods

The proband (Fig. 1), a 2-year-old girl, her parents complained that she has poor eyesight in both eyes and could not accurately grasp objects. She was unable to comply with the detailed eye examination. Under the guidance of
the paediatrician, the opportunity for examination was obtained through oral anaesthesia. Her parents and sister underwent detailed eye examinations, including binocular corrected visual acuity, slit lamp examination, fundus photography, macular and optic disc OCT scanning, and electroretinogram (ERG).

Five millilitres of peripheral blood was obtained from each of the 4 subjects (II5, II8, III1, and III2) and collected in EDTA tubes for DNA extraction. The panel (463 genes related to ocular diseases) in next-generation sequencing (NGS) was used to capture the target gene. Then, Sanger sequencing was performed to validate the variants from 22 candidate genes. The transcript used to identify the variant in the CRB1 gene was NM_201253.

Results
The proband’s parents came from two unrelated families, with no consanguineous or inbreeding. Except for the proband, neither parent had a family member with similar eye disease (Fig. 1a).

After panel capture, 22 candidate genes remained. Primers were designed for each candidate gene, PCR was performed, and then, first-generation Sanger sequencing was used to verify the target gene. Finally, we obtained the target co-isolation gene in this family. Sequencing chromatograms: the proband shows a homozygous variant in the CRB1 gene, nucleotide 1499 changed from a cytosine to guanine (c.1499C>G) homozygous variant, resulting in a nonsense variant of amino acids (p. S500*), her parents and sister show a heterozygous variant at the same site. (Fig. 1b).

The proband’s eyes showed horizontal pendulum nystagmus. On examination, her eyes were in a normal position, the cornea and lens were clear, fundoscopy showed that the colour of the optic disc in both eyes was light, and the blood vessels from both eyes were thin and narrow (Fig. 1c). The pigmentation of the retina at the posterior pole was peppery and salt-like, and the macular area was a mass of lesions with much pigmentation. Her 5-year-old sister’s fundus is normal, and the same is true for her parents.
Table 1  Clinical examination data

| Patient | Gender | Age | Nucleotide amino acid | Homozygous/heterozygous | UCVA OD | CVA OD | Corneal optical refection | Nystagmus | Globe retraction |
|---------|--------|-----|-----------------------|-------------------------|---------|-------|---------------------------|-----------|-----------------|
| II:5    | M      | 34  | c.1499C>G (p.S500*)   | Heterozygous            | 1.0     | 1.0   | 1.0                       | Normal    | −               |
| II:8    | F      | 28  | c.1499C>G (p.S500*)   | Heterozygous            | 0.6     | 0.7   | 1.0                       | Normal    | −               |
| II:8    | F      | 28  | c.1499C>G (p.S500*)   | Heterozygous            | 0.6     | 0.6   | 0.8                       | Normal    | −               |
| III:2   | F      | 2   | c.1499C>G (p.S500*)   | Heterozygous            | 0.6     | 0.6   | 0.8                       | Normal    | −               |

Features of LCA8 and unaffected relatives
UCVA uncorrected visual acuity, CVA corrected visual acuity, OD right eye, OS left eye, +: positive, −: negative

In our study, the proband’s eye examinations and genetic tests were consistent with the diagnosis of LCA. The homozygous variant in the 6th exon of CRB1: nucleotide 1499 changed from cytosine to guanine (c.1499C>G), resulting in a nonsense variant of amino acids (p. S500*), which has not been reported before. The proband’s parents and sister had heterozygous variation at this site. According to the ACMG (American College of Medical Genetics and Genomics) guidelines, the variant was preliminarily determined to be pathogenic: PVS1 + PM2 + PM3_Supporting (hom). PVS1: This variant is a zero-effect variant (nonsense variant), which may lead to loss of gene function; PM2: This variant frequency in the database of the normal population (1000g2015aug_all, ESP6500si, GnomAD_Genome_ALL, GnomAD_Genome_EAS, etc.) is “-”, which means the variant was not detected; PM3_Supporting (HOM): This variant is a homozygous rare variant. No correlation of this locus was reported in the literature database. No pathogenicity analysis results were found in the ClinVar database. Our study expands the spectrum of CRB1 variants causing LCA.

We used the ScanProsite tool (https://prosite.expasy.org/scanprosite/) to examine the secondary structure of the CRB1 protein. The nonsense variant c.1499C>G (p. S500*) is in the laminin G domain profile 485–670: score = 32.931. L, Yang, et al. also reported a nonsense variant c.1576C>T(p. R526X) in this domain [6]. Laminin G is an approximately 180 amino acid long domain found in a large and diverse set of extracellular proteins. It often occurs in multiple copies, probably serving as general protein interaction domains that bind target proteins and other macromolecules, such as carbohydrates. In most proteins, the precise function of the laminin G domain is unknown. A large number of ligands in the G domain of laminin have been reported, including heparin, sulfatides, integrins, dystroglycan, nidogen, and fibulin. In neurexin, the G domain is known to bind neurexophilins, α-latrotoxin and neureligins [7, 8].

Another anatomical feature of LCA includes decreased thickness in different layers, especially in the outer nuclear layer (ONL), loss of integrity in the ellipsoid zone, and disorganized macular atrophy [9]. Unfortunately, the proband we reported was too young to cooperate with optical coherence tomography (OCT) and ERG examination, so we could not analyse the clinical features of these two aspects.

LCA caused by CRB1
In 2004, Hanein et al. [10] reported a comprehensive mutational analysis of all known genes in 179 unrelated LCA patients, including 52 familial and 127 sporadic cases. The results showed that variants were identified in 47.5% of patients. GUCY2D appeared to account for most LCA cases in their series (21.2%), followed by CRB1 (10%), RPE65 (6.1%), RPGRIP1 (4.5%), AIPL1 (3.4%), TULP1 (1.7%), and CRX (0.6%). Three years later, Francesca Simonelli et al. [11] analysed 95 patients in Italy with LCA. They identified some novel variants that occurred frequently in the RPE65 (8.4%), CRB1 (7.4%), and GUCY2D (5.2%) genes. Through a detailed ophthalmic evaluation of patients with the variant, they found that CRB1 variants were associated with reduced retinal thickness and a coarsely laminated retina (by OCT). In London, Henderson, R.H., et al. acquired DNA samples from 250 probands with LCA/early childhood-onset retinal dystrophy (EORD). They analysed using the LCA chip, and CRB1 variants were identified in 21 probands [12]. Corton et al. enrolled 404 Spanish patients in the study, 114 of which suffered from LCA and 290 from EORP (early-onset RP). Their study revealed that 11% of Spanish patients carried variants in CRB1, ranging from 9% of EORP to 14% of LCA cases. More than three-quarters of the variants identified were first described in their study [13].

Liping Yang et al. [6] used 18 cases presenting with LCA to identify disease-causing variants. They reported compound heterozygous variants of the CRB1 gene, which included three novel heterozygous variants:
c.3059delT (p. M1020Sfs*1), c.3460T>A (p. C1154S), and c.4207G>C (p. E1403Q). Hosono et al. reported variants of LCA- and inherited retinal dystrophy (IRD)-associated genes in 34 Japanese families, which is the first study to conduct a next-generation sequencing (NGS)-based molecular diagnosis of a large Japanese LCA cohort and achieved a detection rate of approximately 56%. Their results showed that the most frequently mutated genes were CRB1, NMMAT1, and RPGRIP1 [14]. Recently, Zhu et al. [15] enrolled 37 patients with strictly defined LCA in a cohort of IRD in ten years (2009–2019). Their results revealed that the CRB1 gene occupied a greater proportion (27%) of associated LCAs in the western Chinese population.

CRB1 variants are a common cause of LCA, and related variants include substitution, deletion, duplication and insertion. Table 2 lists the variants in LCA caused by CRB1, which include variant types, sites, corresponding amino acid changes and regions in recent years. These results are for readers’ verification and reference.

“-”: not applicable

To date, a total of 76 CRB1 variants have caused LCA. Furthermore, it has been reported that variants in CRB1 are responsible for 7.4%-27% of LCA in different populations. The pathogenic variants were mainly substitution and deletion, including duplication, insertion, which reflected the richness of variant types (Table 3). The variant sites of LCA8 were mainly concentrated in exons 6, 7 and 9 of CRB1, and clear pathogenic sites were found in all exons except exons 4, 5 and 10, indicating the universality of variant regions (Table 4). The reported cases involved more than 10 countries and regions, including China, England, Japan, Spain and Italy, which also showed that the global coverage of LCA caused by CRB1 is extensive.

**Other diseases of retinal dystrophy caused by CRB1 variants**

In addition to LCA, variants in CRB1 are associated with several other diseases of retinal dystrophy: Rosa Riveiro-Alvarez, et al. [27] reported an early-onset RP phenotype in a Spanish family caused by the Nonsense CRB1 c.2843G>A(p. C948Y) variant. Two CRB1 substitution variants, c.3991C>T(p. R1331C) and c.4142C>T(p. P1381L), were reported to illustrate a novel presentation of macular dystrophy caused by CRB1 variants by Stephen H. Tsang et al. [28]. Arif O. Khan et al. uncovered a homozygous CRB1 variant c.80G>T(p. C27F) in three siblings with childhood cone-rod dystrophy and macular cystic degeneration in a family [29]. Ajoy Vincent et al. reported biallelic variants (p. G123C and p. C948Y, p. I167_G169del and p. R764C) in CRB1 in two families caused autosomal recessive familial foveal retinoschisis, which may be the mildest end of the spectrum of CRB1-related diseases [30]. Benjamin K. Ghiam et al. reported that a novel variant c.4014T>A in CRB1 was related to retinal degeneration and may portend a poor prognosis for CME responsiveness to therapy [31].

**Discussion**

LCA is the earliest and most severe hereditary retinopathy, in which the function of cone-rod cells in both eyes is completely lost at birth or within one year after birth, leading to congenital blindness in infants. The majority of cases are caused by autosomal recessive inheritance. Typical characteristics of LCA include early and severe reduction of vision associated with nystagmus, photophobia, sluggish or absent pupillary responses, finger pressure on eyeballs, fundus appearance, ranging from normal, maculopathy, to typical RP-like abnormalities, and electroretinogram showed that A and B waves were flat and even severely reduced to nondetectable. It can also be accompanied by keratoconus, hyperopia, developmental delay and nervous system abnormalities [32].

In some cases/reports, there are many similar clinical features between LCA and early-onset RP, and even the diagnosis is ambiguous [33]. Early-onset RP is usually considered to be a relatively milder form, in which patients do not have a congenital onset of visual impairment. We could distinguish the following phenotypes: LCA, early onset retinal degeneration; RP, presence of preservation of the para-arteriolar retinal pigment epithelium and Coats-like vasculopathy [34].

To date, 28 genes involved in the pathogenesis of LCA [35]. CRB1 belongs to LCA8. The CRB1 gene maps to chromosome 1q31.3 and is composed of 12 exons; the longest isoform consists of 1,406 amino acids. This gene encodes a protein that is similar to the Drosophila crumb protein and localizes to the inner segment of mammalian photoreceptors. In Drosophila, crumbs localize to the stalk of the fly photoreceptor and may be a component of the molecular scaffold that controls proper development of polarity in the eye [36], and CRB1 has been found to be important in maintaining cellular polarity [37].

In the mouse retina, CRB1 is expressed in the inner segment of the photoreceptors and Muller cells to maintain adequate morphogenesis and polarity in retinal development [38]. Therefore, CRB1 gene variants often lead to a variety of retinal dystrophies, including retinitis pigmentosa (RP), LCA, and macular dystrophy. Approximately 9–17% of LCA cases have been related to CRB1 variants, which is especially higher in the Chinese population [39, 40]. A wide variety of visual acuity was noted in patients with variants in CRB1, ranging from 20/30 to NLP [10, 41].
| Exon | Variant type | DNA change | Amino acid change | Region | References |
|------|--------------|------------|-------------------|--------|------------|
| Ex1  | Substitution | c.2T>C     | p.M1T             | Japanese | Hosono et al. [14] |
| Ex1  | Substitution | c.70+2T>A  | –                 | Chinese  | Zhu et al. [15] |
| Ex2  | Substitution | c.107C>G   | p.S36*            | Pakistan | McKibbin et al. [16] |
| Ex2  | Substitution | c.424G>T   | p.G142*           | uncertain | Beryozkin et al. [17] |
| Ex2  | Substitution | c.471C>A   | p.C157*           | Chinese  | Zhu et al. [15] |
| Ex2  | Duplication  | c.481dupG  | p.A161Gfs*8       | Spanish  | Corton et al. [13] |
| Ex2  | Deletion     | c.498_506del| p.I167_G169del    | England  | Ahmed et al. [18] |
| Ex2  | Deletion     | c.613_619del| p.I205Sfs*13      | Spanish  | Corton et al. [13] |
| Ex2  | Substitution | c.614T>C   | p.I205T           | England  | Henderson et al. [12] |
| Ex3  | Substitution | c.664G>A   | p.S222R           | Chinese  | Li et al. [19] |
| Ex3  | Duplication  | c.696dupT  | p.L232fs*4        | Japanese | Hosono et al. [14] |
| Ex3  | Duplication  | c.733dupG  | p.A245Gfs*16      | Japanese | Hosono et al. [14] |
| Ex3  | Substitution | c.866C>T   | p.T289M           | Italian  | Simonelli et al. [11] |
| Ex3  | Substitution | c.998G>A   | p.G333D           | Korea    | Moon et al. [20] |
| Ex6  | Deletion     | c.1334_1740del| p.C445Yfs*8     | Japanese | Hosono et al. [14] |
| Ex6  | Substitution | c.1405T>G  | p.C469G           | Chinese  | Zhu et al. [15] |
| Ex6  | Substitution | c.1429G>A  | p.G477R           | Chinese  | Yang et al. [6] |
| Ex6  | Substitution | c.1499C>G  | p.S500*           | Chinese  | this study |
| Ex6  | Duplication  | c.1567dupC | p.L523fs*28       | Japanese | Hosono et al. [14] |
| Ex6  | Substitution | c.1576C>T  | p.R526*           | Chinese  | Yang et al. [6, 14] |
| Ex6  | Substitution | c.1604T>C  | p.L535P           | Spanish  | Corton et al. [13] |
| Ex6  | Substitution | c.1678C>G  | p.H560D           | Chinese  | Zhu et al. [15] |
| Ex6  | Substitution | c.1690G>T  | p.D564Y           | Spanish  | Corton et al. [13] |
| Ex6  | Substitution | c.1750G>T  | p.D584N           | Uncertain | Hanein et al. [10] |
| Ex6  | Substitution | c.1831T>C  | p.S561P           | Chinese  | Yang et al. [6] |
| Ex6  | Substitution | c.1841G>T  | p.G614V           | Chinese  | Chen et al. [21] |
| Ex6  | Deletion     | c.1842delT | p.G614del         | Uncertain | Beryozkin et al. [17] |
| Ex6  | Substitution | c.1903T>C  | p.S635P           | Chinese  | Li et al. [19] |
| Ex6  | Substitution | c.2107G>T  | p.E703*           | Iran     | Saberi et al. [22] |
| Ex6  | Substitution | c.2128G>C  | p.E710Q           | Uncertain | Hanein et al. [10] |
| Ex6  | Substitution | c.2128+1G>A | -                  | Iran     | Saberi et al. [22] |
| Ex7  | Substitution | c.2222T>C  | p.M741T           | Uncertain | Hanein et al. [10] |
| Ex7  | Deletion     | c.2227delG | p.V743fs*11       | Spanish  | Corton et al. [13] |
| Ex7  | Substitution | c.2234C>T  | p.T745M           | Chinese  | Yang et al. [6] |
| Ex7  | Deletion     | c.2244delG | p.S749del         | Spanish  | Corton et al. [13] |
| Ex7  | Duplication  | c.2276_2279dupCTTA | p.S749fs*33 | Iran     | Saberi et al. [22] |
| Ex7  | Substitution | c.2290C>T  | p.R764C           | Uncertain | Hanein et al. [10] |
| Ex7  | Substitution | c.2309G>T  | p.G770V           | Spanish  | Corton et al. [13] |
| Ex7  | Substitution | c.2401A>T  | p.K801*           | Italian  | Simonelli et al. [11] |
| Ex7  | Substitution | c.2479G>T  | p.G827*           | Uncertain | Hanein et al. [10] |
| Ex7  | Substitution | c.2536G>T  | p.G846*           | Hungarian | Vamos et al. [23] |
| Ex7  | Substitution | c.2548G>A  | p.G850S           | England  | Henderson et al. [12] |
| Ex7  | Substitution | c.2555T>C  | p.I852T           | Uncertain | Hanein et al. [10] |
| Ex7  | Deletion     | c.2676delG* | p.K892Nfs*95      | England  | Henderson et al. [12] |
| Ex8  | Substitution | c.2677-2A>C | –                  | Chinese  | Lin Li et al. [24] |
| Ex8  | Deletion     | c.2678-2682del | p.S895fs*14 | Uncertain | Beryozkin et al. [17] |
| Ex8  | Substitution | c.2688T>A  | p.C896*           | Spanish  | Corton et al. [13] |
| Ex8  | Substitution | c.2714G>A  | p.R905Q           | Chinese  | Zhu et al. [15] |
| Ex9  | Substitution | c.2843G>A  | p.C948Y           | Polish   | Skorczyk et al. [25] |
Among LCA, RPE65 variants were almost always associated with normal macular thickness, as assessed by OCT, whereas CRB1 variants were associated with reduced retinal thickness and a coarsely laminated retina. Fundus abnormalities were more heterogeneous in carriers of CRB1 variants. In fact, some scholars observed salt-and-pepper retinal dystrophy in younger patients and subsequently massive spicular and not nummular pigmentation at the posterior pole, which was reported to be a phenotypic feature of carriers of CRB1 variants[11]. Saloni Walia et al. [42]. Through a multicentre retrospective observational study with 169 patients with LCA, variants in RPE65 (LCA-Type II) and CRB1 (LCA-8) may be associated with a relatively better VA in early life compared with other gene variants. The onset of the symptoms of LCA after the age of 1 year is also associated with an overall better VA prognosis.

### Table 2 (continued)

| Exon | Variant type | DNA change | Amino acid change | Region | References |
|------|--------------|------------|-------------------|--------|------------|
| Ex9  | Substitution | c.2843G>T  | p.C948F           | Uncertain | Hanein et al. [10] |
| Ex9  | Insertion    | c.2853,2854insT | p.A952fs*972       | Uncertain | Hanein et al. [10] |
| Ex9  | Substitution | c.2945C>A  | p.T982K           | Chinese | Zhu et al. [15] |
| Ex9  | Substitution | c.3002T>A  | p.I1001N          | Spanish | Corton et al. [13] |
| Ex9  | Substitution | c.3017C>A  | p.S1006Y          | Chinese | Zhu et al. [15] |
| Ex9  | Substitution | c.3023T>G  | p.L1008*          | Chinese | Zhu et al. [15] |
| Ex9  | Deletion     | c.3059delT | p.M1020S5*        | Chinese | Yang et al. [6] |
| Ex9  | Substitution | c.3068T>G  | p.L1023R          | Japanese | Hosono et al. [14] |
| Ex9  | Substitution | c.3074G>T  | p.S1025I          | Uncertain | Hanein et al. [10] |
| Ex9  | Substitution | c.3152G>A  | p.W1051*          | Spanish | Corton et al. [13] |
| Ex9  | Substitution | c.3218T>A  | p.L1073Q          | Chinese | Zhu et al. [15] |
| Ex9  | Substitution | c.3221T>C  | p.L1074S          | Chinese | Lin Li et al. [16] |
| Ex9  | Substitution | c.3290T>A  | p.L1097Q          | Chinese | Zhu et al. [15] |
| Ex9  | Substitution | c.3299T>C  | p.I1100T          | Spanish | Corton et al. [13] |
| Ex9  | Substitution | c.3307G>A  | p.G1103R          | Italian | Simonelli et al. [11] |
| Ex9  | Substitution | c.3320T>G  | p.L1107R          | Uncertain | Hanein et al. [10] |
| Ex9  | Deletion     | c.3345delT | p.G1115fs*1140    | Uncertain | Hanein et al. [10] |
| Ex9  | Substitution | c.3466G>T  | p.D1166Y          | Uncertain | Hollander et al. [26] |
| Ex9  | Substitution | c.3482A>G  | p.Y1161C          | Spanish | Corton et al. [13] |
| Ex9  | Duplication  | c.3542dupG | p.C1181Wfs*12     | England | Henderson et al. [12] |
| Ex11 | Substitution | c.3879G>A  | p.W1293*          | Uncertain | Hanein et al. [10] |
| Ex11 | Substitution | c.3961T>A  | p.C1321G          | Uncertain | Hanein et al. [10] |
| Ex11 | Deletion     | c.3988delG | p.E1330fs*1340    | Uncertain | Hanein et al. [10] |
| Ex11 | Deletion     | c.4000delG | p.V1334Wfs*7      | Spanish | Corton et al. [13] |
| Ex12 | Substitution | c.4005+1G>A | –               | Chinese | Zhu et al. [15] |
| Ex12 | Substitution | c.4013+1G>T | –               | Uncertain | Hollander et al. [21] |
| Ex12 | Deletion     | c.4121,4130del | p.R1374fs*1397     | Uncertain | Hanein et al. [10] |

### Table 3 Types and proportion of CRB1 variants causing LCA8

| Types of variants | Substitution | Deletion | Duplication | Insertion |
|-------------------|--------------|----------|-------------|-----------|
| Count             | 56           | 13       | 6           | 1         |
| Percentage        | 73.7%        | 17.1%    | 7.9%        | 1.3%      |

### Table 4 Numbers and proportion of CRB1 exon variants causing LCA8

| Exon | Ex1 | Ex2 | Ex3 | Ex4 | Ex5 | Ex6 | Ex7 | Ex8 | Ex9 | Ex10 | Ex11 | Ex12 |
|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|
| Count | 2   | 7   | 5   | 0   | 0   | 17  | 13  | 4   | 21  | 0    | 4    | 3    |
| Percentage | 2.6% | 9.2% | 6.6% | 0   | 0   | 22.4% | 17.1% | 5.3% | 27.6% | 0   | 5.3% | 3.9% |
Conclusions

LCA is one of the earliest and most severe forms of inherited IRD. Patients suffer from severe visual impairment during childhood, with their vision continuously deteriorating, the final outcome of which is usually complete loss of vision by their thirties or forties[43]. Therefore, it is very important to find an effective treatment. Albert et al. provided an entirely new dimension in ocular therapeutics for gene therapy to LCA2. Patients with LCA2 who received AAV2.hRPE65v2 by subretinal injection showed evidence of improvement in retinal function, pupillary light reflex, and reduction in nystagmus. These clinical trials are approaches to the treatment of LCA and possibly other forms of retinal degeneration[44].

However, much is still unknown about the pathogenesis of LCA. With the improvement of next-generation sequencing technology and the application of various molecular biological means, research on corresponding cell functions, the identification of gene subtypes and the establishment of animal models have greatly promoted our understanding of LCA. These latest advances provide a steady stream of evidence for a better understanding and treatment of LCA in the future. These findings may be useful for faster gene diagnosis, prenatal testing, the development of potential gene therapies, and for improving the understanding of the molecular pathogenesis of LCA.

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Author contributions

WD and TZ carried out the experiments and drafted the manuscript. HJ and MZ prepared the figures and tables. L2 and MH designed and funded this study. All authors read and approved the final manuscript.

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Availability of data and materials

The relevant data were generated during this study and included in this article. Raw sequence data were not available in this article, as no datasets were generated during the current study. The corresponding author Liwei Zhang (dizhangliwei@163.com) should be contacted if someone wants to request the data from this study.

Declarations

Ethical approval and consent to participate

This study was performed in agreement with the Declaration of Helsinki. It was reviewed by the research unit’s professional ethics committee, and informed consent was obtained and signed by the investigator. All experimental protocols were approved by the Affiliated Hospital of Yunnan University, and methods were carried out in accordance with relevant guidelines and regulations, including any relevant details. Informed written consent was taken from all participants and legal guardians of children.

Consent for publication

Written informed consent was obtained from the guardians (parents) of the patients, and they consented to the publication of the study. The guardian (parent) of the patients consented for their medical information to be published.

Competing interests

The authors declare that they have no competing interests.

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