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Full Length Article

A novel *RP1* truncating mutation that causes autosomal dominant retinitis pigmentosa (ADRP)

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ABSTRACT

Background: Retinitis pigmentosa (RP) is a genetically and clinically heterogeneous group of hereditary degenerative disorders affecting approximately one in every 4000 people worldwide. Abnormalities in the retina's photoreceptors can cause night blindness or even complete vision loss. Retinitis Pigmentosa 1 (RP1), also known as the oxygen-regulated protein-1, is a microtubule-associated protein (MAP) that organizes the outer segment of the photoreceptor. Besides, mutations in the *RP1* gene are associated with dominant or recessive form of RP. This study aims to identify the potential pathogenic genes in Chinese RP patients and to elucidate the association relationship between the mutant gene and the phenotypes.

Methods: Multiple ophthalmic examinations, whole-exome sequencing, sanger sequencing, and *in silico* analysis were performed to evaluate the clinical features and pathogenic genes in a five-generation Chinese family diagnosed with RP.

Results: Our findings revealed a novel truncating mutation c.2015_2018del p. (Lys672Argfs*9) in *RP1* that may result in the translation of a protein with deleterious effects on photoreceptors. Therefore, resulting in autosomal dominant retinitis pigmentosa (ADRP).

Conclusions: This study broaden the range of genetic mutations associated with *RP1* in ADRP and make a valuable contribution to the ongoing endeavors aimed at characterizing the molecular aspects of Chinese ADRP. Future studies would pay more attention in determining the characterization of the mutantations in *RP1* gene and the relationship between genotype and phenotype in RP patients.

1. Introduction

Retinitis pigmentosa (RP) is the prevailing inherited retinal disorder, distinguished by the gradual deterioration of rod and cone photoreceptor cells.[1] RP is heterogeneous clinically and genetically that affects 1 in every 4000 people worldwide.[2] RP initially manifests as night blindness and subsequently progresses to peripheral visual field constriction, ultimately resulting in central visual loss and potential legal blindness.[1] The characteristic ocular changes in RP encompass the deposition of pigmented bone spicules in the retina, the narrowing of retinal arterioles, and the pale appearance of the optic disc. Throughout the course of RP, other visual abnormalities such as cataract, glaucoma, refractive errors, atrophy of the retinal pigment epithelium cells (RPE) and maculopathy may occur. Mutations in genes functioning mainly in the retina may result in typical RP, while mutant proteins that have functioning in diverse cells may cause syndromic RP.[1–5]

As a genetic disorder, different familial RP cases show different modes of inheritance: autosomal dominant retinitis pigmentosa (ADRP, 15%–25%), autosomal recessive retinitis pigmentosa (ARRP, 5%–20%), X-linked retinitis pigmentosa (XLRP, 5%–15%) and unknown type (40–50%) (Fig. 1 A).[6] At present, 75 identified genes have been recognized as contributors to RP (RetNet, the Retinal Information Network, updated March 27, 2024; https://sph.uth.edu/retnet/). Among these, a total of 31 distinct genes have been identified as potential causes of

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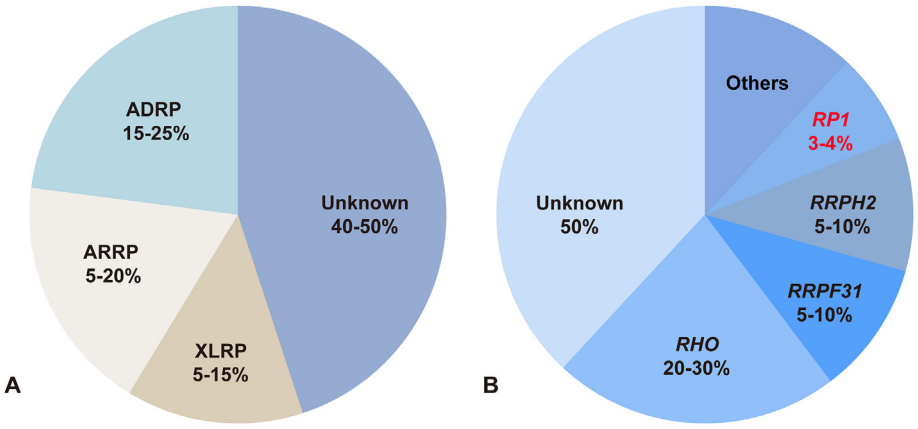

Fig. 1. Pie chart illustrating the proportion of hereditary mode of retinitis pigmentosa (RP) as well as causative genes in autosomal dominant retinitis pigmentosa (ADRP). (A) The inheritance of RP consists four patterns. (B) Estimated relative contribution of genes to ADRP. ADRP: autosomal dominant retinitis pigmentosa; ARRP: autosomal recessive retinitis pigmentosa; XLRP: X-linked retinitis pigmentosa.

ADRP, with notable associations found for *RHO*, *PRPF31*, *PRPH2*, and *RP1* genes in relation to RP (Fig. 1 B).[7] The RP1, also known as oxygen-regulated protein 1, is situated on chromosome 8q12.1. It comprises four exons and encodes a protein composed of 2156 amino acids that is primarily expressed in the retina.[8] *RP1* is a photoreceptor-specific protein that is specifically localized to the connecting cilium and axoneme of photoreceptors. Its primary role is to preserve the structural integrity of cilia and contribute to signal transduction processes within the photoreceptors (Fig. 2). The *RP1* also plays a vital role in outer segment orientation and the misalignment of discs caused by *RP1* mutations resulting in photoreceptor cell death.[9] Moreover, the utilization of mutant mice with targeted modifications in the *RP1* gene offers valuable in vivo evidence regarding the functional role of RP1.[10] The malformation and disorganization of photoreceptor outer segments, mislocalization of rhodopsin, and progressive degeneration of photoreceptors were observed in the *RP1* gene knockout mice, indicating the essential role of *RP1* the in morphogenesis of photoreceptor outer segments. Mutations in the *RP1* gene account for approximately 5.5% of ADRP cases and 1% of ARRP cases.[1] These mutations primarily involve truncation of the *RP1* protein. However, the precise mechanism by which these *RP1* truncating mutations lead to cell death remains unclear. In addition, the majority of *RP1* mutations are reported on exon 4, and the symptoms caused by various mutations are diverse.[11] Therefore, it is necessary to conduct a gene-sequencing diagnosis for RP patients. Whole exome sequencing (WES) techniques offer a robust approach for precise genetic disorder diagnosis. This method not only strengthens clinical diagnoses but also opens new avenues for gene-based therapeutic interventions.[12,13]

In this investigation, we unveiled a previously undocumented truncating mutation c.2015_2018del p. (Lys672Argfs*9) within the *RP1* gene as observed in an RP-affected Chinese family with concomitant subluxated lens and posterior subcapsular cataract. The WES analysis indicated that both affected individuals carried heterozygous mutations, whereas the normal individuals did not carry out the mutation. We further elucidated the possible functional changes caused by this mutation through bioinformatics analysis.

2. Materials and methods

2.1. Proband, pedigree and clinical assessment

We enrolled a Chinese family with RP spanning five generations, diagnosed based on established ophthalmological criteria, from the Second Affiliated Hospital of Zhejiang University. All procedures adhered the principles outlined in the Declaration of Helsinki. All the subjects had family history and detailed ophthalmologic examinations, including slit lamp biomicroscopy, ultrasound biomicroscopy (UBM), best corrected visual acuity (BCVA), intraocular pressure (IOP), wide angle fundus photograph, and optical coherence tomography (OCT). Written informed consent was obtained from all participants, and the

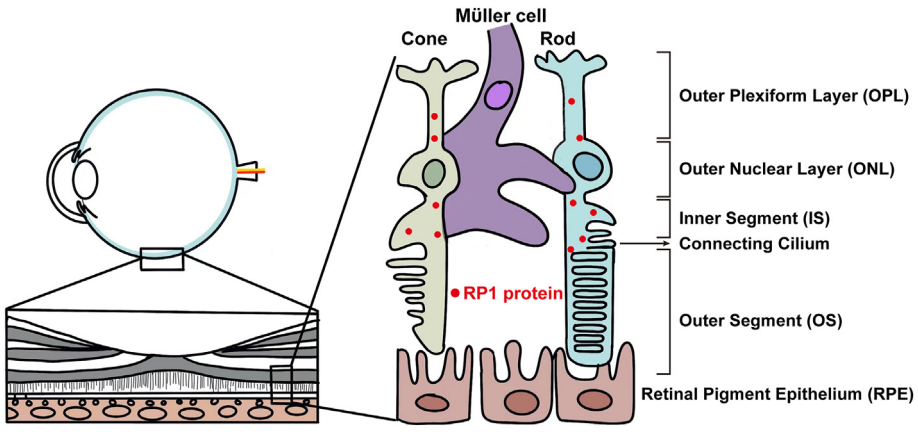

Fig. 2. Schematic representation of the human photoreceptors and the localization of the RP1 protein. The posterior retina is locally magnified. The cone, Müller cell, rod and retinal pigment epithelium cells (RPE) are represented in green, purple, blue and brown. The RP1 protein is located in the connecting cilium of rod (red arrow).

ethical clearance for the consent procedure was granted by the ethics committee of the Second Affiliated Hospital of Zhejiang University.

2.2. Whole exome sequencing

WES analysis was conducted on individuals IV-3, IV-6, and V-2 following previously described protocols.[14–17] Genomic DNA was extracted from peripheral leukocytes of two patients and one relative using the Blood Genome Column Medium Extraction Kit (Kangweishiji, China). The Roche Nimble Gen Seq EZ Exome Enrichment Kit V2.0 and Seq EZ Exome Enrichment Kit V2.0 capture probes (Roche, USA) were employed to prepare the whole exome DNA library. Subsequently, sequencing was performed on the Illumina NovaSeq 6000 series sequencer (PE150). Raw data underwent quality control procedures, including adapter removal, low quality reads filtering, and other quality assessments. Mapping was accomplished using the Burrows Wheeler Aligner (BWA) with the human genome reference (hg19), and mutation calling was executed using GATK software. Samtools and Pindel were used to call Single Nucleotide Polymorphisms (SNPs) and indels, respectively. The clean data were filtered according to the quality of the sequencing. Nonsynonymous substitutions and SNPs with Minor Allele Frequency (MAF) lower than 5% were filtered using SIFT. Whenever applicable, familial segregation analysis was conducted for identified mutations. Suspected candidate mutation sites were amplified using PCR and validated by Sanger sequencing analysis, utilizing the primers GCCTCTTCCTTTGGATATTTCTAACTT (forward) and TAAAGAATTTGCCCTGGTTGTAGC (reverse).

2.3. Mutation bioinformatics analysis

The identified mutation was evaluated based on the criteria outlined by the American College of Medical Genetics and Genomics (ACMG) to assess its potential pathogenicity.[18] The loss of function of the mutation was evaluated using the PVS1 ACMG/AMP mutation criterion.[19] Multiple sequence alignments were performed using MEGA 11 software to analyze sequence alignments. The NP_006260.1 sequence was utilized as a reference for oxygen-regulated protein 1 isoform 1 (*Homo sapiens*), NP_035413.1 for oxygen-regulated protein 1 isoform 1 (*Mus musculus*), XP_035026983.2 for oxygen-regulated protein 1 (*Hippoglossus stenolepis*), AAK58443.1 for retinitis pigmentosa 1 protein (*Canis lupus familiaris*), XP_030634220.1 for retinitis pigmentosa 1 like 1 protein (*Chanos chanos*). In addition, we applied the SOPMA tool to analyze the secondary structure of the RP1 protein.[20]

3. Results

The study included a Chinese family spanning five generations, consisting of 27 members. Among them, five individuals (two affected and three unaffected) were selected for further investigation. The pedigree was consistent with autosomal dominant inheritance (Fig. 3). Clinical data for the two affected members can be found in Table 1, while genotyping results are provided in Table 2.

The index patient (Fig. 3, IV-3) was a 56-year-old male who reported experiencing night blindness since the age of approximately 10 years old. This individual complained of blurred vision for five years and progressive exacerbation for one year. Upon examination, his BCVA was both Finger Count/Before eye. Examination revealed the presence of posterior subcapsular cataracts, along with iridodonesis and phacodonesis, which were due to lens subluxation (Fig. 4 A). The shallow anterior chamber (AC) and complete closure of the anterior angle were evident (Fig. 4 B). Elevated IOP was observed, with readings of 22 mm Hg in the right eye (OD) and 30 mm Hg in the left eye (OS) (Table 1). Elevated intraocular pressure was due to lens subluxation. Funduscopic examinations unveiled widespread bone spicule pigment deposits, retinal arteriole attenuation, waxy pallor of the optic disc, retinal atrophy, and an enlarged cup-to-disc ratio of 0.6 in both eyes (OU) (Fig. 4 C). As a tool reflecting RP progression, the OCT also showed the bilateral disappearance of the ellipsoid zone (EZ), and thinner retina as well as the choroid (Fig. 4 D).

The elder cousin of the proband (Fig. 3, IV-6) was a 61-year-old male who complained of bilateral poor vision for over 10 years and nyctalopia since childhood. His visual acuity was less than 0.06 OU. Ophthalmic examination revealed bilateral cataracts, shallow AC, and subluxated

Table 1
Clinical features of affected individuals with *RP1* gene mutation in the family.

	IV-3		IV-6	
	OD	OS	OD	OS
Age (years)	56	–	61	–
Age of onset of night blindness (years)	10	–	10	–
Sex	M	–	M	–
BCVA (LogMAR)	< 0.06	< 0.06	HM	HM
IOP (mmHg)	22	30	11	15
C/D ratio	0.6	0.6	0.6	0.6
ACD (mm)	2.18	2.31	–	–
AL (mm)	25.72	25.75	23.11	23.00

M: male; BCVA: best corrected visual acuity; LogMAR: logarithm of the Minimum Angle of Resolution; HM: hand motion; IOP: intraocular pressure; C/D ratio: cup to disc ratio; ACD: anterior chamber depth; AL: axial length.

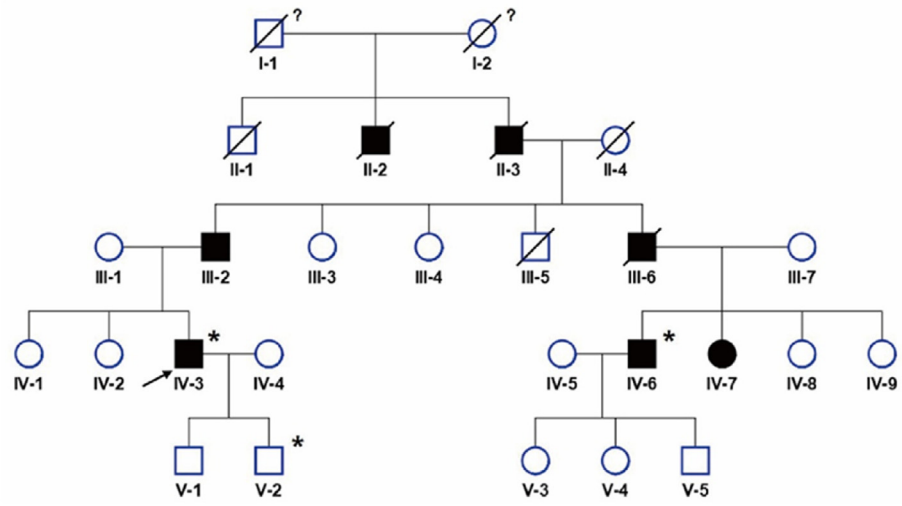

Fig. 3. Pedigree of the RP patient's family. Segregation analysis of *RP1* mutation in a pedigree represents an autosomal dominant inheritance pattern. Squares and circles represent males and females respectively. Closed and open symbols indicate affected members and unaffected subjects. The arrow denotes the proband. Family history was negative for consanguinity. The slash symbol indicates that the subject was deceased. The asterisk shows the individual underwent both clinical and genetic analyses. The question mark indicates the ophthalmic history is not available.

Table 2
Genotyping Results according to the Sanger sequencing.

	Gene	Nucleotide variation	Genotype	Clinical diagnosis
IV-3	*RP1*	c.2015 (exon4) _2018del (exon4) del AGAA	Heterozygous	Retinitis Pigmentosa
IV-6	*RP1*	c.2015 (exon4) _2018del (exon4) del AGAA	Heterozygous	Retinitis Pigmentosa
V-2	*RP1*	–	Homozygous	Normal

lens with normal IOP (Fig. 4A and B, Table 1). Fundus photography revealed clinical manifestations similar to the proband (Fig. 4 C). The EZ area only exists around the fovea, the retina and choroid adjacent to the area become thinner (Fig. 4 D). Both RP patients underwent surgical procedures in both eyes, including phacoemulsification, posterior chamber intraocular lens implantation, and capsular tension ring implantation to ensure proper fixation. After the operation, there was a marked improvement in vision, and the IOP of the two patients decreased to normal.

The other three unaffected family members (V-1, V-2, and V-4) had no night blindness, blurred vision, and other abnormal ophthalmic complaints. None of them had any indication of RP after dilated fundus photograph. To validate the diagnoses, the whole exomes sequencing of the two RP patients (IV-3, IV-6) and one son of the proband (V-2) was performed (Fig. 3, Table 2). The average read depth for 98.9% of the targeted sequences reached 20x. Genetic testing unveiled a heterozygous frameshift mutation c.2015_2018del p. (Lys672Argfs*9) within the fourth exon of the *RP1* gene (NM_006269, #OMIM: 180100). Sanger sequencing confirmed the absence of this mutation in the unaffected individual (V-2) (Fig. 5). Based on ACMG guidelines, the identified mutation was classified as likely pathogenic, with PVS1-strong and PM2 evidence categories (Table 3). Segregation analysis demonstrated that this novel frameshift mutation co-segregated with the RP phenotype in the affected families. Conservative sequence analysis revealed high conservation at the mutation site, suggesting its significant physiological role in evolution (Fig. 6). The truncating mutation resulted in severe disruption of secondary structures in RP1 protein, including alpha helices, extended strands, beta-turns, and random coils (Fig. 7).

4. Discussion

The hereditary retinopathy RP is characterized by progressive visual dysfunction, which has negative impact on patients as well as society. The disease severity depends mainly on the inheritance patterns, and patients with ADRP have milder symptoms than those with ARRP or XLRP. As for heterozygous carriers of ADRP, the unaffected allele may synthesize protein to maintain visual function. Along with the disease

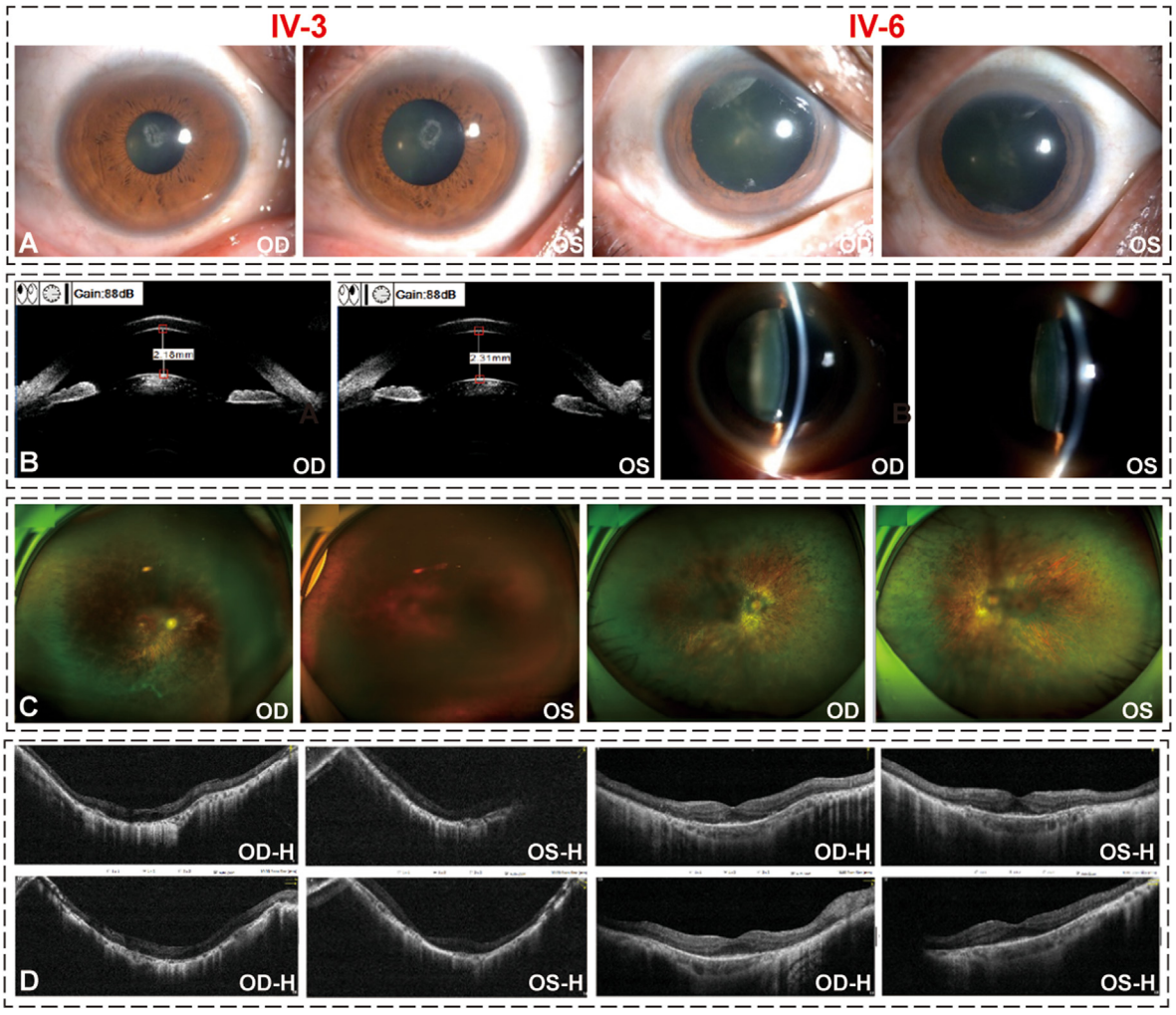

Fig. 4. Ophthalmic examinations of the two RP patients (Left: IV-3 Right: IV-6; All data are presented OD first and then OS. (A) Slit lamp examination showing signs of bilateral cataract. Preoperative pupil dilation was performed on IV-6. (B) Shallow anterior chamber observed by ultrasound biomicroscopy (UBM) and slit lamp biomicroscopy of IV-3. (C) Fundus photograph of the affected proband IV-3 (Left) and his elder cousin IV-6 (Right) showing typical RP changes. (D) The optical coherence tomography (OCT) was performed horizontally and vertically. H: horizontal; V: vertical.

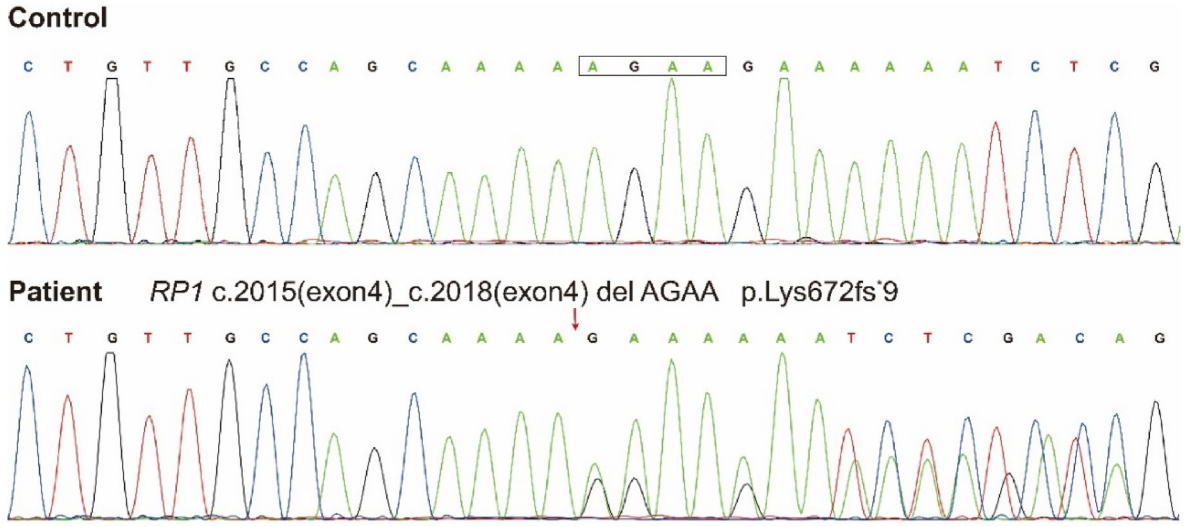

Fig. 5. Sanger sequencing validation of the *RP1* mutation. Sanger sequencing revealed a novel frameshift mutation of *RP1* gene in the proband was identified c.2015_2018del p. (Lys672Argfs*9).

Table 3
Mutation table for the frameshift mutation of *RP1* gene.

Gene	Chromosome	Nucleotide	Amino Acid	Prediction type (ACMG)	Genotype
RP1	Chr 8: 55538457-55538460	c.2015_2018del	p.Lys672Argfs*9	Likely Pathogenetic	Heterozygous

ACMG: The American College of Medical Genetics and Genomics.

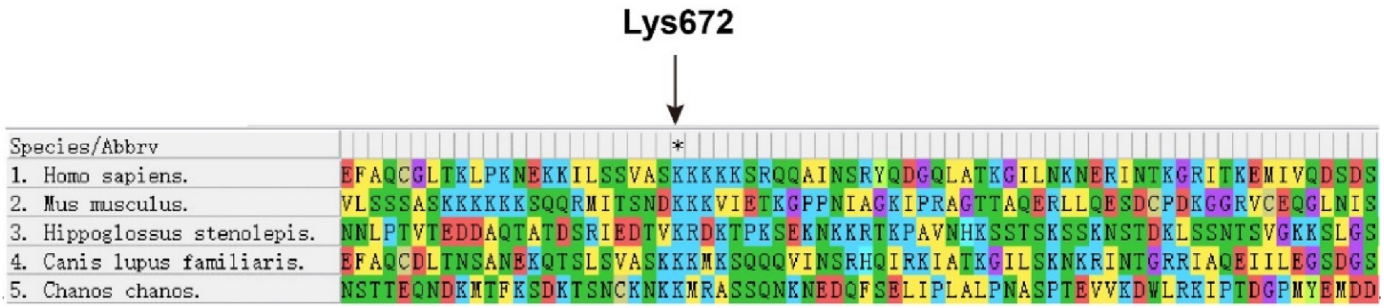

Fig. 6. Sequence alignments of RP1 proteins from various species with GeneDoc. The black arrow indicated that the Lys672 amino acid was conservative.

progress, the hypermetabolic photoreceptor cells decompensate and result in the corresponding clinical symptoms. Variability exists in the age at which symptoms appear, the rate of disease progression, and the severity of symptoms, which can be attributed to different genetic mutations.

RP1 is a gene associated with both ADRP and ARRP. The proteins encoded by *RP1* are primarily found in the connecting cilia of rod and cone photoreceptors, where they likely play a role in maintaining the structure and orientation of the cilia (Fig. 2).[8,21] Additionally, these proteins are involved in the transportation of newly synthesized outer segment proteins from the inner segment to the site of disc membrane assembly through the cilia. Thus, any toxic products caused by *RP1* mutation may interfere with the signal transmission of photoreceptor signaling. The RP1 protein exhibits sequence similarity with the neuronal microtubule-associated protein doublecortin. The latter plays a crucial role in stabilizing cytoplasmic microtubules.[22] In addition, the amino sequence from residues 486 to 635 shares homology with BIF and is critical for normal photoreceptor morphogenesis.[8] Certain studies have suggested that truncations occurring within or immediately after the BIF motif or RP1 lead to the production of detrimental proteins, resulting in the development of ADRP.[23] Additionally, other researchers have proposed four distinct classes of truncating mutations within the *RP1* gene, each with varying implications for the underlying cause of RP.[24] The amino acid sequence was divided into separate regions with various effects on the pathogenicity of RP. Mutations categorized as Class II are situated within the region spanning from p.500 to p.1053 in exon 4 (Fig. 8). Mutations occurring in this region are not susceptible to nonsense-mediated mRNA decay (NMD) and can result in the production of truncated proteins. These truncated proteins have the potential to impair photoreceptor function, leading to cell death and exacerbating the progression of RP. The majority of previously reported *RP1* truncating mutations associated with ADRP were located in the hot spot region between p.500 to p.1053.[11,25–33] Interestingly, our findings identified a novel truncating mutation that has not been reported before. The novel 4bp deletion in exon4 c.2015_2018del p. (Lys672Argfs*9) was considered to be the cause of a frameshift in the *RP1* gene, accompanied by subsequent production of a truncated protein denoted as p. Lys672Argfs*9. The novel mutation of *RP1* in this pedigree was located after the BIF motif and was consistent with the above Class II mutations (Fig. 8). In our study, further bioinformatics analysis revealed that the heterozygous frameshift mutation in *RP1* triggered ADRP in the pedigree. Sequence consistency analysis indicated that the novel mutation affects

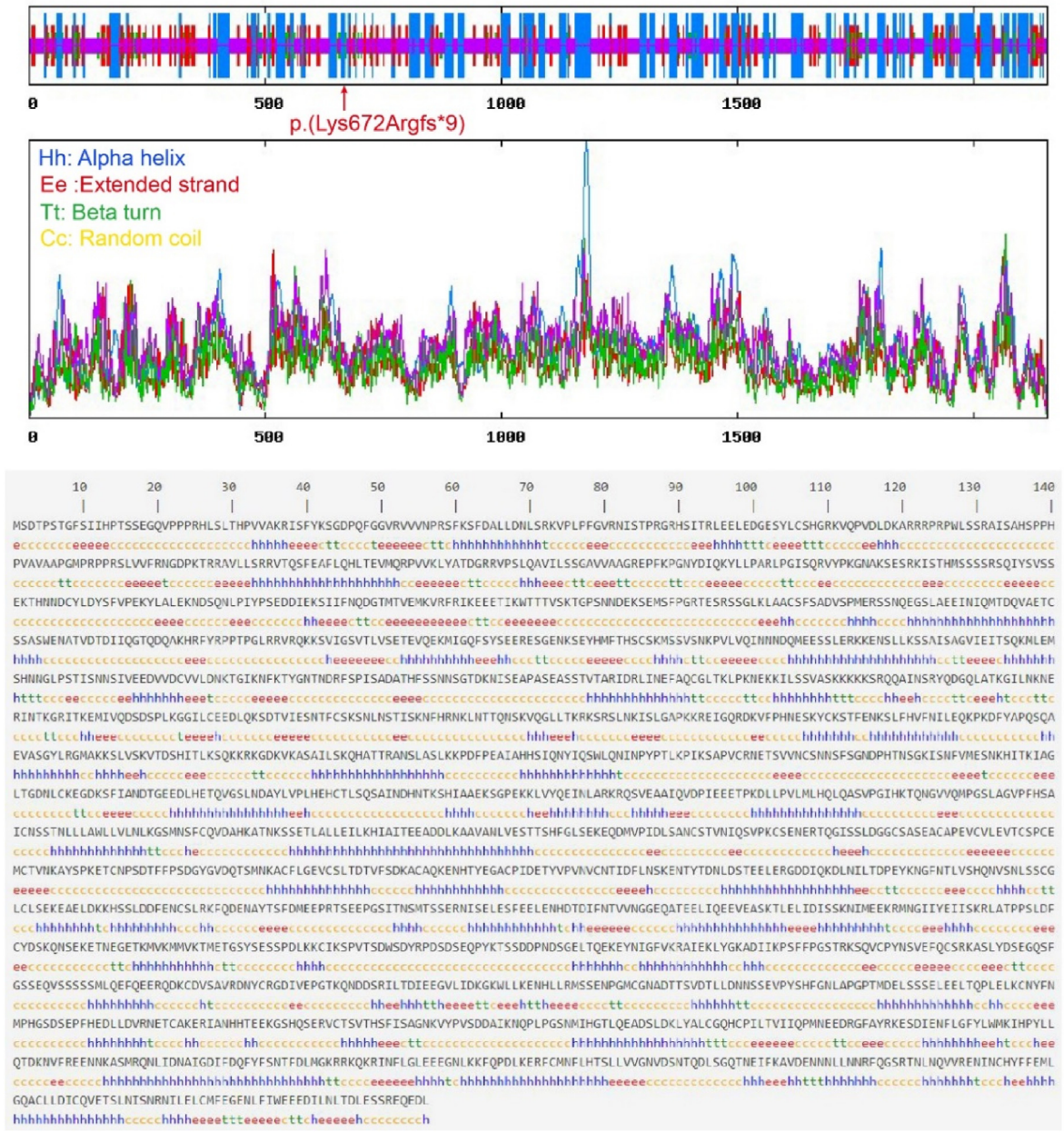

Fig. 7. The predicted secondary structure of RP1 by the SOPMA tool. The RP1 protein was composed of alpha helix (30.8%), beta fold (15.03%), beta turn (4.96%), and random coli (49.21%). The truncating mutation (p. Lys672Argfs*9) may disrupt the most of secondary structures.

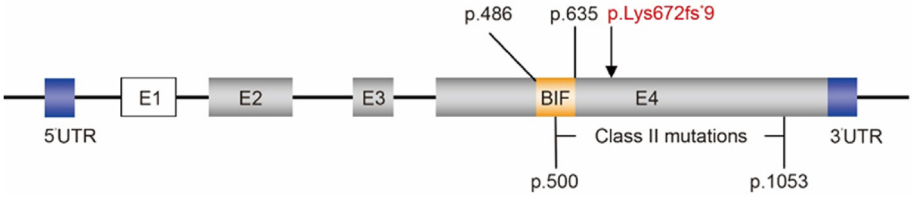

Fig. 8. RP1 gene and identified mutations. The novel mutation of *RP1* gene c.2015_2018del p. (Lys672Argfs*9) identified in this study belongs to Class II mutations (p.486-p.635). E = exon, UTR = untranslated region, BIF = the *Drosophila melanogaster* domain.

highly conserved sites that likely play crucial roles in essential physiological functions (Fig. 6). Furthermore, analysis of the secondary structure revealed that the truncating mutation results in the loss of most func-tional protein domains in a clear and evident manner (Fig. 7). Bioinformatics analysis indicated that the novel truncated mutation participated in the occurrence and development of diseases.

Ongoing endeavors aim to comprehensively understand the molecular aspects of RP resulting from *RP1* gene mutations. Previous investigations have revealed that the RP1 protein localizes to the connecting cilia, bridging the inner and outer segments of

photoreceptors, and is likely involved in protein transportation and the maintenance of cilia structure.[22] Early studies employed gene-targeting techniques to generate mice carrying a mutant form of *RP1*, referred to as *RP1-mycalle*.[9] Light and electron microscopy examinations demonstrated that homozygous mutant mice experienced rapid-onset retinal degeneration, while heterozygous mice retained relatively healthy photoreceptors. These findings indicated that the truncated RP1-myc protein lacked functionality and did not exert a dominant negative effect on photoreceptors. In $RP1^{-/-}$ mice, the number of rod photoreceptors gradually declined, and both rod and cone outer segments displayed morphological abnormalities.[10] Furthermore, the rod electroretinogram (ERG) amplitudes of $RP1^{-/-}$ mice were significantly smaller compared to $RP1^{+/+}$ mice, with the $RP1^{+/-}$ mice exhibiting intermediate responses. Above findings verified that RP1 protein was involved in transporting proteins in photo-receptors and required for the morphogenesis of photoreceptors. Interestingly, it has also been suggested that despite containing putative nuclear localization domains, the RP1 protein is unlikely to function as a transcription factor involved in photoreceptor development. To explore this further, some researchers have utilized microarray analysis to examine gene expression profiles in retinas from both $RP1^{+/+}$ and $RP1^{-/-}$ mice, conducting dynamic observations during the postnatal period.[34] These investigations uncovered distinct molecular phenotypes across multiple biological pathways. It was discovered that *RP1* activates JNK cascades via rhodopsin and Rac1, and the decrease in JNK signaling cascades in $RP1^{-/-}$ mice could trigger subsequent photoreceptor cell death by reducing the activity of c-Jun. Other studies involving animal models demonstrated that RP1-Q662X mice exhibited progressive degeneration of photoreceptors leading to disorganization of photoreceptor outer segments. Notably, this phenotype could be prevented by restoring the expression of a normal amount of RP1 protein.[35] To sum up, RP1 is essential for maintaining visual function and may be involved in the RP development through different mechanisms. However, due to the technical limitations and long experimental periods, the precise mechanism underlying cell death in RP resulting from various mutations in the *RP1* gene remains elusive.

In this Chinese pedigree, in addition to the common ocular signs of RP, both affected individuals were diagnosed with lens subluxation, shallow AC, and posterior subcapsular cataract. Ectopia lentis is commonly attributed to factors such as trauma, pseudoexfoliation syndrome, Marfan's syndrome, and other similar conditions.[36,37] Further examinations were performed in both patients to rule out the above causes of lens luxation. Currently, several cases from different countries have also been reported that RP patients had lens subluxation, leading to secondary elevated intraocular pressure.[38–42] However, the detailed mechanism has not been elucidated yet. It is speculated that zonular instability and lens fiber disorganization with altered ultrastructure may be the cause angle closure in ACG.[39] Furthermore, the thickened and enlarged lens, as well as the loose suspensory ligament, might cause shallow AC by moving the lens forward.[43] A posterior subcapsular cataract occurs in about 45% of RP patients, and patients can still benefit from surgery, although the macula has been involved.[44–46] The visual prognosis appeared great after cataract extraction for both the proband and his elder cousin, which is in accordance with the above findings. Some determined that those with ADRP showed a greater prevalence compared with ARRP, X-linked RP, and sporadic RP. Moreover, cataracts may be present even at a younger age in ADRP patients.[44] This reminds clinicians that when a patient is genetically diagnosed with ADRP and has blurred vision due to cataracts, personalized surgery should be performed even when the retina is affected by RP. This assists in rapidly improving the quality of life of patients.

5. Conclusions

In summary, we examined two Chinese RP cases with concomitant lens subluxation and posterior subcapsular cataract based on ophthalmic examination and gene sequencing. Mutations in the *RP1* gene are not frequently observed among Chinese patients with ADRP. Our findings broaden the genetic mutation spectrum of *RP1* in ADRP cases. In addition to contributing to ongoing efforts toward characterizing the structure-function relationship of RP1 in Chinese ADRP patients at the molecular level. Future studies will determine the relationship between the genotype and phenotype.

Study approval

The authors confirm that any aspect of the work covered in this manuscript that involved human patients was conducted with the ethical approval of all relevant bodies and the study was performed in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University (approval number:2023-1168).

Author contributions

The authors confirm contribution to the paper as follows: Conception and design of study: XJC, HJ; Data collection: WW, YZ; Analysis and interpretation of results: XJC, YZ; Drafting the manuscript: YZ, WW; All authors reviewed the results and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

ADRP	autosomal dominant retinitis pigmentosa
ARRP	autosomal recessive retinitis pigmentosa
MAP	microtubule-associated protein
XLRP	X-linked retinitis pigmentosa
WES	Whole-exome sequencing
RPE	retinal pigment epithelium cells
BCVA	best corrected visual acuity
LogMAR	logarithm of the Minimum Angle of Resolution
HM	hand motion
IOP	intraocular pressure
C/D	ratio cup to disc ratio
ACD	anterior chamber depth
AL	axial length
AC	anterior chamber
UBM	ultrasound biomicroscopy
ERG	electroretinogram
OCT	optical coherence tomography
EZ	ellipsoid zone
SNPs	Single Nucleotide Polymorphisms

MAF	Minor Allele Frequency
ACMG	The American College of Medical Genetics and Genomics
NMD	nonsense-mediated mRNA decay

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