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ARTICLE

Sector Retinitis Pigmentosa caused by mutations of the *RHO* gene

Ting Xiao[1] · Ke Xu[1] · Xiaohui Zhang[1] · Yue Xie[1] · Yang Li[1]

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Abstract

Background Sector retinitis pigmentosa (RP) is an atypical form of RP in which only one or two quadrants of the retina are involved. The objectives of this study were to report the results of a molecular screening of five unrelated Chinese patients with sector RP and describe the clinical features observed in patients with *RHO* mutations.

Methods Five probands that were clinically diagnosed with sector RP were recruited for genetic analysis. They underwent ophthalmic examinations, including best corrected visual acuity, fundus examination, visual field examinations, and electroretinography. A combination of molecular screening methods, including the targeted next-generation sequencing (TES) and sanger-DNA sequencing of *RHO*, were used to detect mutations. *In silico* programs were used to analyze the pathogenicity of all the variants.

Results Three *RHO* missense mutations (p.T17M, p.L31Q, and p.G106R) were identified in the five unrelated probands. The novel mutation p.L31Q was detected in three unrelated probands. All patients showed bilateral and symmetrical retinal degeneration in the inferior retina and had relatively good visual acuity. Patients with the p.L31Q mutation showed phenotypic variability and variable penetrance.

Conclusion Our results indicate that *RHO* mutations are also common in Chinese patients with sector RP. The *RHO* gene should be given priority during mutation screening analysis for Chinese patients with sector RP.

Introduction

Sector retinitis pigmentosa (RP) is an atypical form of RP in which only one or two quadrants of the retina are involved [1, 2]. This disorder is characterized by regionalized areas of retinal pigment epithelium (RPE) atrophy, attenuated vessels, and bone spicule pigmentation, usually in the inferior quadrant, although affected regions in the superotemporal or superior quadrants have also been reported [1–3]. Sector RP is a stable or slowly progressive disorder that can appear with a subnormal or normal electroretinogram (ERG) and visual field defects of varying extent, depending on the affected regions of retina [1–3]. Patients may present with nyctalopia or mild visual loss, but they usually have relatively good central visual acuity unless their RP is combined with cystoid macula edema or angle-closure [1–3]. Most sector RP cases can be inherited in an autosomal dominant pattern and are caused by mutations of *RHO* [4–9].

The *RHO* gene, comprised of five coding exons, encodes a rod-specific protein called rhodopsin that belongs to a superfamily of seven transmembrane G-protein-coupled receptors. Rhodopsin, which has 348 amino acids, has a structure composed of three regions: the cytoplasmic, transmembrane (TM), and intradiscal domains [10–12]. To date, more than 150 distinct mutations (http://www.hgmd.cf.ac.uk/ac/gene.php?gene = RHO) have been identified at various sites on the *RHO* gene, and the majority of these are missense mutations (Human Gene Mutation Database, HGMD). Most mutations of the *RHO* gene have been identified in adRP patients [13, 14]. Rare mutations have been detected in autosomal recessive RP patients or dominant congenital stationary night-blindness patients, [14]. demonstrating the phenotypic variability caused by *RHO* mutations. Several *RHO* mutations have been described as being responsible for sector RP, and all of them are missense mutations, most of which are located in the intradiscal domain [4–9, 15–18].

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✉ Yang Li
yanglibio@aliyun.com

[1] Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology & Visual Sciences Key Lab, Beijing, China

In addition to *RHO* mutations, mutations of the *CDH23* and *USH1C* genes have recently been reported to cause sector RP [19, 20]. Mutations of *CDH23* and *USH1C* typically cause Usher syndrome (USH), an autosomal recessive disorder characterized by visual impairment because of RP, sensorineural hearing loss, and variable vestibular dysfunction. Mutations of these two genes can cause non-syndromic hearing loss as well. Unlike sector RP patients with mutations of the *RHO* gene, two sector RP patients with compound heterozygous mutations of *CDH23* and *USH1C* also had hearing defects[19, 20] which suggests that they should be diagnosed with an atypical form of USH, one inherited in an autosomal recessive pattern.

The purpose of the current study was to report the results of a molecular screening of five unrelated Chinese patients with sector RP and to describe the clinical characteristic of patients with *RHO* mutations.

Materials and Methods

Patients

This study was approved by the Ethics Committee of Beijing Tongren Hospital and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from each enrolled patient. In this study, five unrelated probands were enlisted from the Genetics Laboratory of the Beijing Institute of Ophthalmology, Beijing Tongren Ophthalmic Center, from 2012 to 2017. Of these probands, only two had a family history of sector RP. All probands underwent detailed ophthalmic examinations, including best-corrected visual acuity with E decimal charts, slit lamp biomicroscopy, color fundus photography (TRC-NW8, TOPCON, Japan), and a visual field (VF) test, either a Humphrey visual field test (Zeiss 750i, Carl Zeiss, Ltd, Germany) or kinetic perimetry (Carl Zeiss 12187, Jena Germany). Some probands underwent full-field ERG examinations (2000NV, Chongqing Guote Medical Equipment Co. Ltd., China) according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standard, fundus autofluorescence (FAF) (Heidelberg OCT SPECTRALIS, Heidelberg, Germany), and optical coherence tomography (OCT) (Heidelberg OCT SPECTRALIS, Heidelberg, Germany or Ivue-100, Optovue Inc., Fremont, CA) examinations. The diagnosis criteria for sector RP were as follows: fundus changes typical of RP in one or two quadrants bilaterally or unilaterally, normal or subnormal ERG, normal or defected visual field corresponding to the affected retinal areas, and the exclusion of any known reasons, such as trauma or infection, for the RP-like appearance of the fundus [1].

Peripheral blood samples were collected from all the probands and their available relatives for genetic analysis. The genomic DNA was then extracted using a genomic DNA extraction and purification kit (Vigorous Whole Blood Genomic DNA Extraction Kit; Vigorous, Beijing, China) based on the manufacturer's protocol.

Targeted exome sequencing

A targeted exome sequencing (TES) panel was developed to capture 188 known inherited retinal degeneration (IRD) genes using GenCap custom enrichment kits (MyGenostics, Beijing) and following the manufacturer's instructions, as described previously. The panel was comprised of approximately 550 kb that covered 2894 exons in total. A list of the target genes for our panel is summarized in Supplementary Table S1. The genomic DNA (1–3 μg) of two patients (019217 and 019717) was fragmented into ~300–450 base pairs and used to capture the targeted genomic sequences. The Illumina library preparation and capture experiments were performed as previously reported [21]. The enrichment libraries were sequenced on an Illumina NextSeq 500 (Illumina, Inc., San Diego, CA, USA) as 100-bp paired-end reads according to the manufacturer's protocol. The raw sequencing data were processed for subsequent bioinformatic analysis. First, the Illumina sequencing adapters and low-quality reads were removed using fastq_mcf software. Then, the duplicated reads were removed using Picard tools (http://broadinstitute.github.io/picard/), and the high-quality reads were aligned with the reference human genome (hg19) using the Burrows-Wheeler Aligner (http://bio-bwa.sourceforge.net/). Finally, the single nucleotide polymorphisms (SNPs) and insertions or deletions (InDels) were called using the Genomic Analysis Toolkit Haplotype Caller. The variants were further annotated by using ANNOVAR and associated with multiple databases, including 1000 genome, ESP6500, dbSNP, ExAC, and an in-house variant database (My Genostics, Beijing). Next, the alternative alleles with <5 reads and/or a frequency <30% were removed to exclude likely false-positive variants.

PCR-based sequencing of the *RHO* gene

All exons and flanking splicing sites of the *RHO* gene were amplified via the PCR in three probands (019768, 019945, and 010418). The primer sequences and related information are same as previously described [22]. PCR amplifications were performed using standard reaction mixtures, and the purified amplified fragments were sequenced using an ABI Prism 373 A DNA sequencer (Applied Biosystems, Foster City, CA, USA). A published cDNA sequence for *RHO*

(GenBank NM_000539) was compared with the sequencing results.

Bioinformatics analysis

Two databases, HGMD (http://www.hgmd.cf.ac.uk/ac/index.php) database and the LOVD database (https://grenada.lumc.nl/LOVD2/eye/home.php), were used to screen for the mutations reported in published studies. The prediction of the pathogenicity of the variants was performed by three in silico programs, including PolyPhen2 (http://genetics.bwh.harvard.edu/pph, in the public domain), Mutation Taster (http://www.mutationtaster.org, in the public domain), and SIFT (http://sift.jcvi.org/, in the public domain). Then, we excluded the variants which had only a minor allele frequency (MAF) >0.1% in any of the databases: 1000 Genomes (http://phase3browser.1000genomes.org), Exome Aggregation Consortium (ExAC, http://exac.broadinstitute.org), and gnomAD (http://gnomad.broadinstitute.org). All the potentially pathogenic variants detected via TES were validated using Sanger sequencing. Finally, co-segregations were conducted if the DNA from the family members was available.

Results

RHO mutations

We identified three heterozygous missense mutations of the *RHO* genes in the five probands (Table 1). Of these mutations, the p.L31Q mutation was first identified in the current study. This novel mutation was predicted to be pathogenic by three in silico analysis programs (Polyphen2, Mutation Taster, and SIFT) and was not found in any of 100 normal controls or any public databases, including the Exome Variant Server, 1000 Genomes Database, and gnomAD. The novel mutation was identified in three unrelated probands (Table 1 and Fig. 1).

Clinical profile

Five unrelated probands harbored a heterozygous disease-causing *RHO* mutation, and co-segregation analyses were performed in two pedigrees (Fig. 1a). Of the five probands, only two patients had obvious symptoms: one complaint about night blindness and another whose visual acuity had gradually decreased. The other three patients were asymptomatic, and the abnormal appearance of their fundus was noted upon routine ophthalmic examination. All patients had a relatively good BCVA range, from 0.4 to 1.0 (Table 1). Color fundus photographs of the five probands revealed bilateral and symmetrical retinal degeneration in the inferior retina that included bone spicule pigmentary changes and vascular attenuation of varying extents. The visual field testing of the four probands showed superior visual field defects of varying extents, while patient 019945 presented a normal result (Table 1, Figs. 1 and 2). The FAF of three probands showed hypofluorescent regions corresponding to the affected retinal areas, with a thick curvilinear band of hyperfluorescence separating the normal central fluorescence from the affected hypofluorescent regions (Figs. 1 and 2). The horizontal cross-scan of the OCT of four probands showed a normal macular appearance. Full-field ERG recordings demonstrated the impairment of rod and cone function to varying degrees (Fig. 3).

Although the three unrelated probands carried the same mutation, p.L31Q, they showed diverse phenotypes. Proband 019217 was a 61-year-old male who had experienced nyctalopia more than 40 years and was diagnosed with angle-closure glaucoma (ACG) in his left eye <1 year ago. At his last examination, in 2012, his BCVA was 1.0 in his right eye and 0.8 in his left eye. A slit lamp examination of his eyes revealed a shallow anterior chamber. Except for regional retinal degeneration, his left eye showed a typical glaucoma optic disc appearance with a 0.9 cup/disc ratio (Fig. 1b). A co-segregation analysis revealed that his three brothers all carried the p.L31Q mutation. However, only two of his brothers (019217–2 and 019217–3) had

Table 1 Clinical featurs of the five probans with *the RHO* mutations

ID	Gender	Age, year		Symptom	Family history	BCVA	Glaucoma	ERG	VF	Mutation
		Exam	Onset			(OD/OS)				
019217	M	61	20	NB	Yes	1.0/0.8	Yes	NA	SD[a]	p.L31Q
019717	M	31	NA	NO	No	0.8/0.4	No	Reduction	SD	p.L31Q
019945	F	32	NA	NO	No	0.9/0.8	No	NA	Normal	p.L31Q
019768	F	50	48	VAD	Unclear	0.6/0.8	No	NA	SD	p.G106A
010418	M	34	NA	NO	Yes	1.0/1.0	No	Reduction	SD	p.T17M

ERG electroretinogram, *BCVA* best corrected visual acuity, *OD* right eye, *OS* left eye, *OU* both eye, *VF* visual field, *M* male, *F* female, *NB* night blindness, *VAD* visual acuity decreased, *N/A* not available, *SD* superior field defect.

[a]inferotemporal visual isle in the left eye; reduction, moderate reduction of cone and rod function

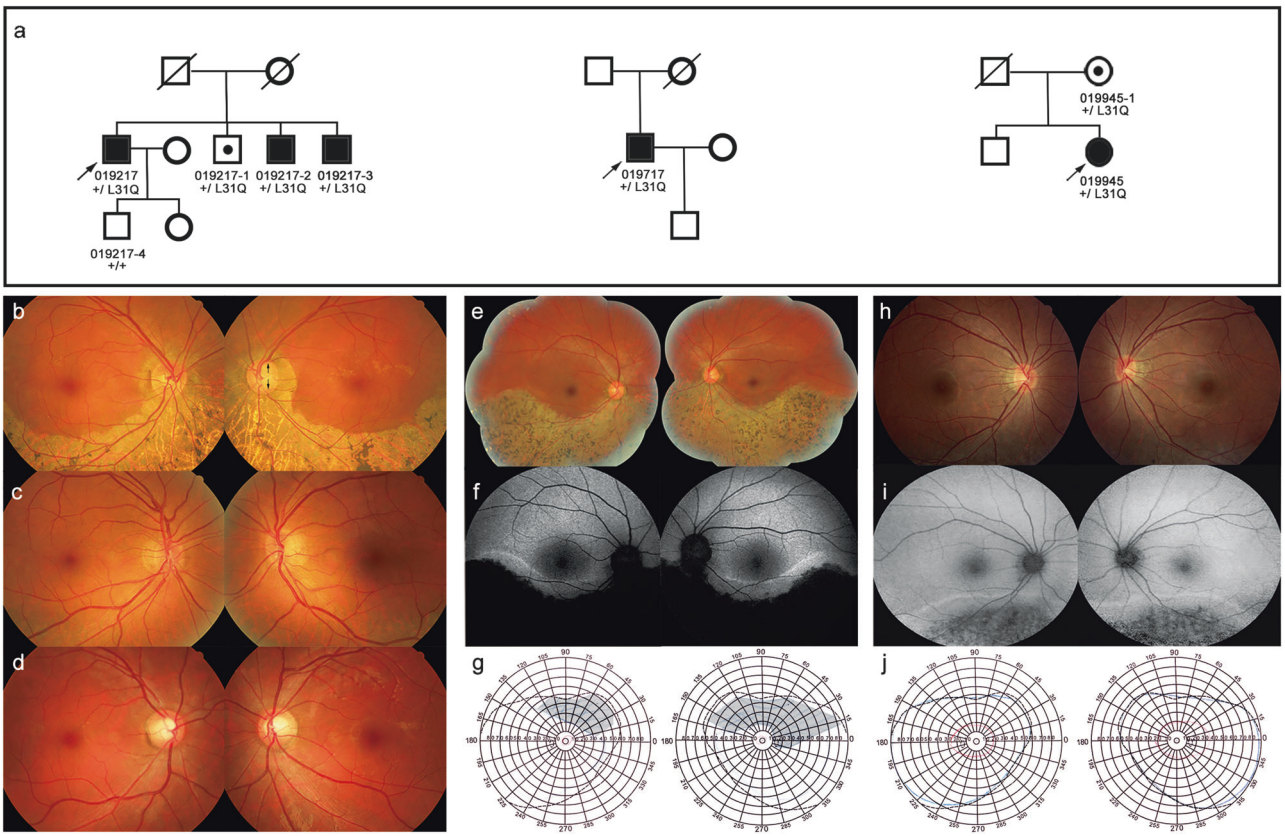

Fig. 1 Pedigrees, fundus appearances, autofluorescence (AF), and visual fields (VF) of three families with sector RP. **a** Pedigrees and segregation analysis (heterozygous mutation p. L31Q in family 019217, 019717, and 019945). Square denote males; circles denote females; solid symbols indicate affected; open symbols indicate unaffected; open symbols with a spot indicate an asymptomatic carrier; slashed symbols indicate deceased; an arrow below the symbol indicates the proband; + indicates wild-type. **b**, **c**, **h** The color fundus (CF) photos of probands 019217, 019717, and 019945 show symmetrical retinal degenerations in the inferior quadrants in both eyes. **b** In addition to the retinal degeneration, CF photo of proband 019217 displays a typical glaucoma cup (black arrows) in the left eye. **c** The CF photo of 019217–1 shows mild RPE changes in the inferior peripheral retina. **d** The CF photo of 019217–4 displays normal fundus appearances. **d**, **i** The AF of proband 019717 and 019945 present symmetrical hypofluorescence areas in the inferior quadrants. **g** The VF of prband 019717 showed the superior visual field defects corresponded to the affected retina. **j** The VF of proband 019945 presents normal visual fields

nyctalopia and superior quadrant visual field defect complaints. The other brother (019217–1) was asymptomatic, and his color fundus photo showed mild RPE changes in the inferior retina (Fig. 1c). Probands 019717 and 019945 also carried the p.L31Q mutation and were both clinically sporadic and asymptomatic. Their ages upon their last examinations were very close. However, their retinal defect areas were quite different. Proband 019717 displayed a large area of retinal degeneration involving almost the entire inferior hemisphere, except the macular region. In contrast, proband 019945 showed small areas of RPE atrophy in the more peripheral inferior retina and had normal visual field results (Fig. 1h–j). Of the five probands, patient 019768, with mutation p.G106R, showed extensive arteriole narrowing in the affected region of the retina and the unaffected inferonasal region (Fig. 2b). Her daughter had suspicious night blindness, but she refused to undergo either ophthalmologic examination or mutation screening analysis.

Discussion

In the current study, we initially performed next-generation sequencing with our IRD panel in two patients with sector RP, and we identified one mutation of the *RHO* gene. Therefore, we performed the sanger-DNA sequencing of *RHO* in the other three patients. Three heterozygous missense mutations were identified in these five unrelated patients. Our results were consistent with the observations of several previous studies suggesting that the majority of sector RP cases may be caused by mutations of the *RHO* gene [2–6, 9, 15–18]. Although mutations of the *USH1C* and *CDH23* genes have been described in two patients with

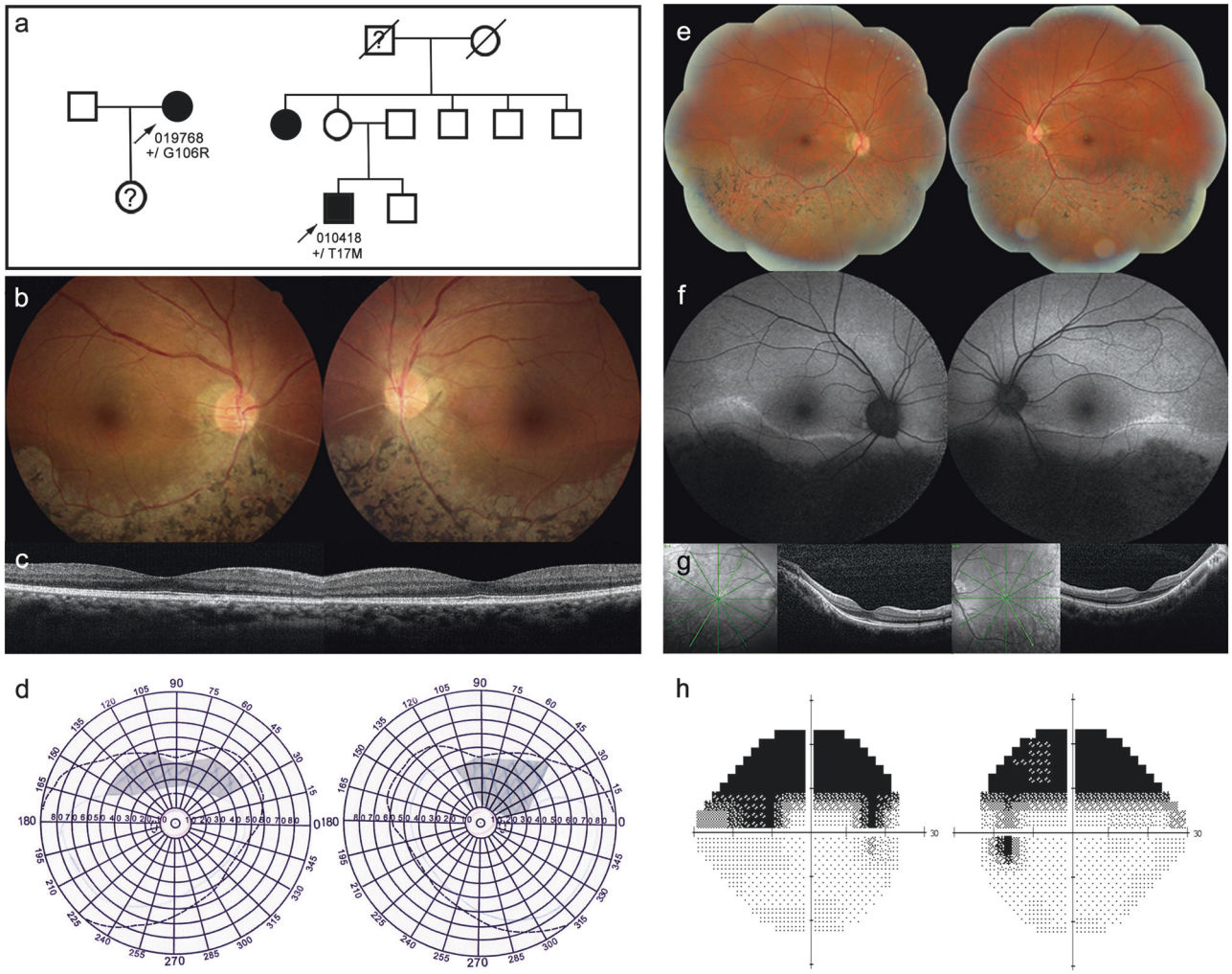

Fig. 2 Pedigrees, fundus appearances, autofluorescence (AF), macular optic coherence tomography (OCT) images, and visual field (VF) of two sector RP families. **a** Pedigrees of family 019768 and 010418 the heterozygous mutations p.G106R and p.T17M, respectively. Square denote males; circles denote females; solid symbols indicate affected; open symbols indicate unaffected; open symbols with an interrogation mark indicate suspect symptomatic; slashed symbols indicate deceased; an arrow below the symbol indicates the proband; + indicates wild-type. **b–d** The color fundus photo, OCT, and VF of proband 019768 show symmetrical retinal degeneration and hypofluorescence areas in the inferior quadrant, normal macular appearances, and the superior visual field defects. **e**, **g**, **h** The color fundus photo, OCT, and VF of proband 010418 present similar changes as described above. **f** The AF of proband 010418 shows symmetrical hypofluorescence areas in the inferior retina

sector RP, those patients also had early-onset hearing defects. Thus, they should be diagnosed with atypical USH [19, 20]. Consistent with our screening results, no patients in the current study had any hearing loss complaints.

Previously, nine *RHO* mutations have been reported to be responsible for sector RP (Table 2) [4–9, 15–18]. Most of these mutations were found in Caucasian patients, but not mutation p.G106R, which was also identified in one Japanese family [17]. It should be noted that the majority of such mutations, including the novel one identified in the current study, are located within the intradiscal domain of rhodopsin. *RHO* mutations have been classified into six categories based on their biochemical and cellular defects, and most of them belong to Class I or Class II [23]. Class I mutations, located exclusively at the C-terminal of the protein, can fold properly but are not correctly transported to the outer segment. Class II mutations, which occur in the intradiscal, transmembrane, and cytoplasmic domains of the protein, lead to misfolded protein being retained in the endoplasmic reticulum. Most of the previously reported mutations belong to Class II, except for two unclassified mutations, p.N15S and p.P170H [23]. Regarding the novel mutation, p.L31Q, we presume that it may have a similar pathogenic mechanism to that of the Class II mutations. However, its precise functional effect remains to be elucidated. Of the three mutations detected in the current study,

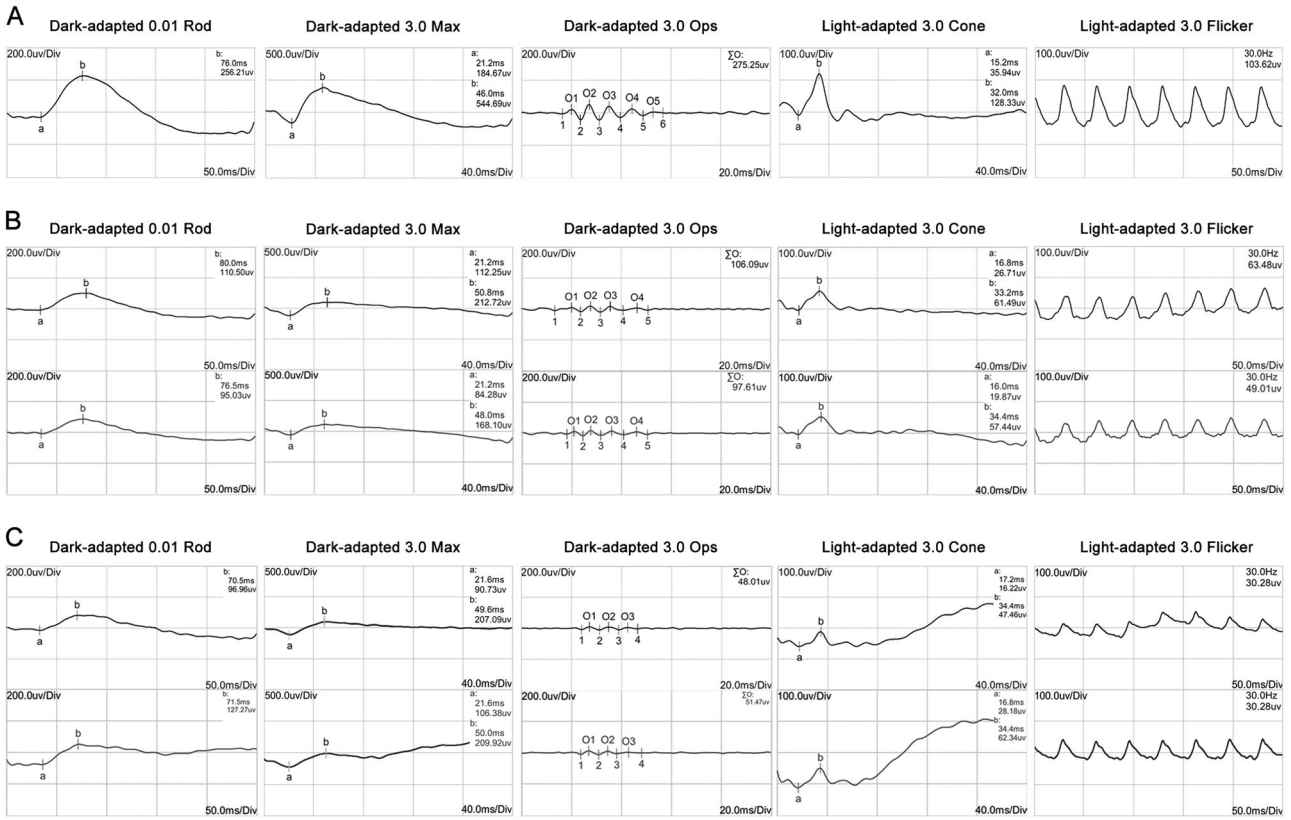

Fig. 3 ERG recording of a normal control (21 years old) and two patients. **a** The ERG of the right eye of the normal control. **b**, **c** The ERG recordings of patient 019717 and 010418 show different extent of defects of rod and cone function. The upper line of responses denotes the right eye, and the lower line denotes the left eye

Table 2 *RHO* mutations identified in sector RP in different ethnics

Exon	Mutation	Domain and structural position	Phenotype	Ethnics	Source
1	N15S	Intradiscal, NH_2 terminal tail	Sector RP	Caucasian	[21]
1	T17M	Intradiscal, NH_2 terminal tail	Sector RP	Caucasian Chinese	[4] This study
1	P23H	Intradiscal, NH_2 terminal tail	Sector/typical RP	Caucasian	[5]
1	P23A	Intradiscal, NH_2 terminal tail	Sector RP	Caucasian	[24]
1	L31Q[a]	Intradiscal, NH_2 terminal tail	Sector RP	Chinese	This study
1	T58R	First transmembrane, helix I	Sector RP	Caucasian	[6] [7]
1	T58M	First transmembrane, helix I	Sector RP	Caucasian	[2]
1	G106R	Intradiscal, between helix II and helix III	Sector/typical RP	Caucasian	[15]
			Sector RP	Japanese Chinese	[14] This study
2	P170H	Forth transmembrane, helix IV	Sector RP	Caucasian	[13]
3	G182S	Intradiscal, between helix IV and helix V	Sector RP	Black Race	[4]

[a]Novel mutation

p.T17M and p.G106R were first detected in Caucasian patients. Later, p.G106R was identified in a Japanese family, [17]. suggesting that these two mutations are hot-spots for sector RP that are geographically widespread. In contrast, p.L31Q, which was found in three unrelated patients in the current study, was not described in patients of any other ethnic background than Chinese. Thus, we speculate that it may be a Chinese-specific mutation. The

mechanism of sector RP remains unclear. Some mutations, such as p.P23H and p.G106R, can cause both typical RP and sector RP (Table 2) [13, 24].

Of the five pedigrees in this study, none showed a clearly autosomal dominant transmitter pattern. This was due to the fact that most patients with sector RP were asymptotic and we did not have a chance to perform detailed clinical examinations for the relatives of the five probands. This was also a limitation of the current study. The probands with the same mutation, as well as the related patients, such as the patients with pedigree 019217, showed phenotypic variability and variable penetrance. This may be related to other genetic and environmental modifiers. Chronic angle-closure glaucoma (ACG) was observed in one proband (019217) with p.L31Q. In a very early study, two sisters with sector RP were found to have ACG. Unfortunately, they did not undergo any mutation screening analysis [3]. In our one previous study, ACG was observed in two related patients with typical RP who carried the p.P347Q mutation [22]. Compared to relatively stable sector RP, ACG can cause more severe visual defects. Therefore, it should receive more attention during clinical evaluations. The relationship between ACG and *RHO* mutations remains unclear.

In conclusion, our results revealed that *RHO* mutations were also common in Chinese patients with sector RP. The *RHO* gene should be given priority during mutation screening analysis for Chinese patients with sector RP.

Summary

What was known before

- RHO mutations have been described as being responsible for sector RP in Caucasion

What this study adds

- Our results indicate that RHO mutations are also common in Chinese patients with sector RP

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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