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ORIGINAL PAPER

Rhodopsin gene mutation analysis in Iranian patients with autosomal dominant retinitis pigmentosa

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Abstract

Purpose Retinitis pigmentosa (RP) is the most common hereditary retinal degeneration and an important cause of visual disability worldwide. Rhodopsin gene is one of the most important genes implicated in autosomal dominant RP (ADRP). In this study, we investigated rhodopsin gene mutations in Iranian patients with ADRP.

Methods Twenty-one patients from 21 unrelated families with a total of 51 affected members were enrolled in this study. After complete history taking, ophthalmic examination and genetic counseling, peripheral blood samples were obtained. Following genomic DNA extraction, all five exons and intron–exon boundaries of *RHO* gene were sequenced using Sanger method. Interpretation of detected variants was carried out using appropriate databases and bioinformatic tools. Novel variants were screened in 150 unrelated healthy subjects.

Results Results of direct sequencing revealed that five of 21 patients (23.8%) had mutation in the rhodopsin gene. Two of them had previously identified p.P347L mutation, and three had novel variants including p.L95P, p.R177K and p.N310K. None of these novel variants were detected in healthy controls. The p.L95P variant was associated with predominantly inferior retinal involvement.

Conclusions Our study showed that mutations of the rhodopsin gene are relatively frequent in Iranian patients with ADRP and could be considered in further researches in the future. The novel p.L95P variant may be associated with a specific pattern of retinal degeneration in this population.

Keywords Retinitis pigmentosa · Rhodopsin · Mutation · Genotype–phenotype correlation

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Introduction

Retinitis pigmentosa (RP) is the most common hereditary retinal dystrophy which leads to visual disability in adulthood in most cases [1]. Because of the structural and functional importance of the rhodopsin protein in rod photoreceptors, any alteration can lead to the rod and subsequently cone degeneration [2]. Mutations in rhodopsin gene (*RHO*) have been reported in 5–30% of patients with autosomal dominant RP (ADRP) and being considered as the most common single gene responsible for RP [3, 4].

More than 110 mutations have been characterized in *RHO* gene; new mutations are emerging along with new studies [5–8]. The first and the most studied mutation, P23H, has been reported to be exclusive to the USA, where a single ancestry might be the origin [9, 10]. It is the cause of about 10–15% of ADRP cases in the USA [11]. Otherwise, P347L has been the most frequent reported mutation in most of the other populations [4, 6, 8].

Mendes et al. [12] proposed that *RHO* mutations can be classified into six classes according to the mechanisms by which they cause retinal degeneration. They also suggested that mutations of each class may be associated with distinct phenotypic expression [12]. Greater susceptibility of the inferior retina has been reported in transgenic mice expressing mutant rhodopsin [13] and more recently in studies on human subjects with specific rhodopsin mutations [14]. This phenomenon has been attributed to light-induced retinal damage which is more in the inferior retina.

We performed this study to investigate the *RHO* mutations among Iranian patients with ADRP and any genotype–phenotype correlation.

Patients and methods

Subjects

In this cross-sectional observational study, patients with the clinical diagnosis of retinitis pigmentosa who had been referred to the Iran RP Center (Tehran, Iran) were reexamined by a retinal subspecialist at Labbafinejad Medical Center (LMC), and diagnosis of RP was verified according to the typical history and clinical findings. Scotopic and photopic full-field electroretinography (ERG) was performed in cases with uncertain clinical diagnosis or atypical presentation. Comprehensive pedigree analyses were then carried out for all families, and the inheritance pattern was determined by a medical geneticist. The inclusion criteria included definite diagnosis of RP and autosomal dominant inheritance pattern which was defined as the presence of affected members in at least 2 consecutive generations in a way that probands had affected parents. Patients with uncertain diagnosis, syndromic RP, sporadic or uncertain inheritance pattern were excluded from the study.

During a comprehensive genetic counseling session, advantages and limitations of the study were thoroughly discussed and a written consent was obtained from all participating families. Peripheral blood samples were taken from the proband and all accessible family members who consented to enroll the study. The Ethics Committee of Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, approved the study. All procedures conformed to the principles outlined in the Declaration of Helsinki.

Direct sequencing

All laboratory procedures were performed at the molecular genetic laboratory of Hope Generation Foundation, Tehran, Iran. Genomic DNA was extracted using standard phenol–chloroform method. All five exons and intron–exon boundaries of *RHO* gene were amplified using the primers shown in Table 1 and were then sequenced using Sanger method. For all detected variants, the allele frequency in known genome reference databases including 1000 genomes, 5000 exomes, exome aggregation consortium (ExAC), dbSNP and disease databases like ClinVar and Human Genome Mutation Database (HGMD) was investigated. Moreover, in silico analysis using bioinformatic prediction tools including PolyPhen-2 (Polymorphism Phenotyping v2), mutation taster, Condel, PROVEAN (protein variation effect analyzer), SIFT (sorting intolerant from tolerant), MA (mutation assessor), M-CAP (Mendelian clinically applicable pathogenicity) and FATHMM (functional analysis through hidden Markov models tool) was carried out for novel variants. The frequency of novel variants in an in-house database comprising of 150 unrelated healthy controls (Iran Variome, http://variome.ir) was also determined. The inclusion

Table 1 Primer sequences for PCR amplification of exons 1–5 of *RHO* gene

Exon	Primer sequence	Product size (bp)
Exon 1	Forward: 5′ AGCTCAGGCCTTCGCAGCAT 3′	558
	Reverse: 5′ GAGGGCTTTGGATAACATTG 3′	
Exon 2	Forward: 5′ GAGTGCACCCTCCTTAGGCA 3′	290
	Reverse: 5′ TCCTGACTGGAGGACCCTAC 3′	
Exon 3	Forward: 5′ CTGTTCCCAAGTCCCTCACA 3′	260
	Reverse: 5′ CTGGACCCTCAGAGCCGTGA 3′	
Exon 4	Forward: 5′ ATGCATCTGCGGCTCCTGCT 3′	379
	Reverse: 5′ CCTGGGAGTAGCTTGTCCTT 3′	
Exon 5	Forward: 5′ ACGTGCCAGTTCCAAGCACA 3′	273
	Reverse: 5′ ATTCTGCACAGGCGCTGCTC 3′	

criterion for healthy controls was no history of visual impairment, especially inherited retinal disease in the normal controls and their relatives.

In case of positive findings, segregation analysis was carried out by investigation of all available samples from affected and unaffected family members for the detected variant in the proband.

Results

Twenty-one patients from 21 unrelated families (51 affected members) with diagnosis of ADRP were enrolled in this study. The patients' mean age was 38.29 ± 10.68 (range 21–57 years), and the mean age at which the first symptoms appeared was 12.38 ± 6.5 (range 6–30 years). Mean of the best spectacle corrected visual acuity (BSCVA) was 0.37 ± 0.39 LogMAR (range 0.05–1.7).

Except 3 patients who had undergone cataract surgery, all of the remaining 18 patients had some degrees of posterior subcapsular cataract in both eyes. In addition, 1+ anterior vitreous cells were noted in all subjects. There was one case of glaucoma (bilateral neovascular glaucoma secondary to retinal vasoproliferative tumor) and two cases of cystoid macular edema with no other systemic and other ocular conditions.

Direct sequencing of *RHO* gene in 21 families revealed previously reported p.P347L mutation in 2 families (families 1 and 2) and novel variants in three families (families 3, 4 and 5). Details of the in silico analysis and the allele frequency of novel variants in genome databases are shown in Table 2.

The mean and standard deviation of LogMAR of visual acuity in patients with and without rhodopsin mutation were 0.46 ± 0.6 and 0.82 ± 0.7, respectively ($P = 0.135$). Except the patient with p.R177K mutation which had bilateral optic atrophy due to multiple attacks of optic neuritis on the basis of multiple sclerosis, the remaining 4 patients with rhodopsin mutation had excellent visual acuity (i.e., better than 20/30). The clinical characteristics of patients with *RHO* gene mutation are summarized in Table 2.

Family 1

As shown in the pedigree of the family (Fig. 1A), the proband was a 29-year-old man (individual 3:7) with history of progressive nyctalopia and decreased vision in his both eyes since childhood. He had undergone bilateral laser epithelial keratomileusis (LASEK) for a 3 diopter myopia when he was 23 years old. His visual acuity was 20/22 in both eyes without any residual refractive errors. On slit-lamp examination, there was mild posterior subcapsular (PSC) cataract and anterior vitreous cells were present. Intraocular pressure was 13 mmHg without using anti-glaucoma medications. Fundus examinations revealed typical findings for RP including waxy disk pallor, vascular attenuation and midperipheral bone spicule-like pigmentations. Humphrey automated visual field test showed severe peripheral field constriction in both eyes. Similar findings were observed in his 50-year-old mother (individual 2:7) and 25-year-old brother (individual 3:8). His grandmother as well as two of his uncles (individuals 1:2, 2:2 and 2:4) had similar symptoms and were diagnosed with RP. Direct sequencing of

Table 2 Probability of pathogenicity of novel variants assessed by different prediction tools

Family no.	*RHO* mutation	Eye	CDVA	Refraction	Age	Onset	Additional ocular findings
1	p.P347L	OD	20/22	Plano	29	13	Mild PSC cataract/OU
		OS	20/22	Plano			LASEK/OU
2	p.P347L	OD	20/50	− 0.50 − 1.75 * 180°	47	14	PE + PIOL/OU
		OS	20/70	− 1.50 − 1.50 * 150°			
3	p.L95P	OD	20/25	+ 0.50 − 2.00 * 115°	26	7	Trace PSC cataract/OU, predominant inferior BS
		OS	20/25	+ 0.50 − 2.00 * 85°			
4	p.R177K	OD	CF	− 1.00 − 0.75 * 10°	37	10	Moderate PSC cataract/OU, bilateral optic atrophy
		OS	CF	− 0.75 − 0.50 * 165°			
5	p.N310K	OD	20/25	Plano	51	12	Mild PSC cataract/OU
		OS	20/25	Plano			

CDVA corrected distant visual acuity, *PSC* posterior subcapsular, *PE* phacoemulcification, *PIOL* posterior chamber intraocular lens, *BS* bony spicule

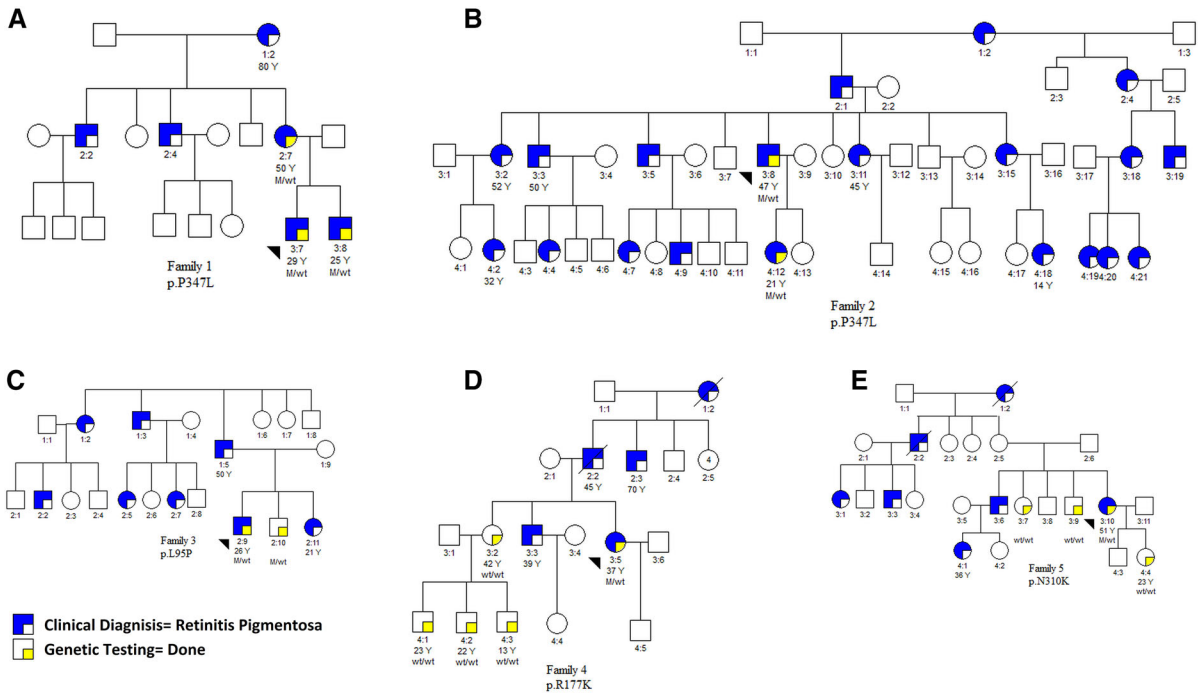

Fig. 1 Pedigrees of the families with positive finding in *RHO* gene. Arrows denote the probands. Genotypes of studied individuals are shown under their corresponding symbols (wt/wt: wild-type alleles; M/wt: heterozygous mutation)

RHO gene revealed c.1040C > T (p.P347L) mutation in the proband and his affected brothers (Fig. 1A).

Family 2

The proband was a 47-year-old man (Fig. 1B, individual 3:8) with history of nyctalopia since adolescence and progressive visual acuity and peripheral field loss since then. He had undergone cataract

surgery (phacoemulsification) with intraocular lens (IOL) implantation 3 years before. BSCVA was 20/50 and 20/70 with refraction of plano − 1.75 × 180° and − 1.50 − 1.50 × 150° in his right and left eyes, respectively. Slit-lamp examination was unremarkable except trace cells in the anterior vitreous. Fundus examination was typical of RP with diffuse midperipheral bone spicules. His pedigree (Fig. 1B) was strongly suggestive of AD inheritance. In direct sequencing of the *RHO* gene, the same mutation as the first family (p.P347L) was detected in the proband and his affected daughter (individual 4:12).

Family 3

The proband was a 26-year-old man (Fig. 1C, individual 2:9) with history of nyctalopia since childhood and decreased visual acuity since 3 years before. BSCVA was 20/25 in both eyes. On slit-lamp examination, trace PSC cataract and anterior vitreous cells were observed. Indirect ophthalmoscopy revealed mild waxy disk pallor with sharp margins. Foveal reflex was absent, and diffuse vascular attenuation and RPE depigmentation were noted. Pigmentary changes as bone spicules were predominant in the inferior retina and sparse in the superior retina (Fig. 2).

Direct sequencing of the *RHO* gene revealed a point mutation in exon 1 (c.284 T > C), which leads to substitution of leucin by proline at amino acid position 95 located in intradiscal portion of the protein (p.L95P). The variant has been registered in GenBank under the accession number of KP734176.

The same variant was found in his unaffected brother (Fig. 1C, individual 2:10). However, re-examination revealed slight RPE depigmentation in inferior midperipheral retina. The best-corrected visual acuity was 20/20 in both eyes with refraction of − 1.50 − 0.75 × 170° and − 2.00 − 0.5 × 10° in the right and left eyes, respectively. Automated 24-2 Humphrey visual field test revealed normal visual field in both eyes. ERG also showed normal recordings in scotopic and photopic conditions in both eyes (Table 3).

Other patients of this family refused to participate in further investigations of this variant, and therefore, segregation analysis could not be performed.

Family 4

As demonstrated in Fig. 1D, the proband was a 37-year-old woman (individual 3:5) with history of nyctalopia since she was 10 years old. She was diagnosed with RP after aggravation of her visual acuity and peripheral field loss when she was 24 years old. She was also a known case of recurrent optic neuritis in the setting of multiple sclerosis (MS) since she was 27 years old. Her visual acuity was counting fingers (CF) and did not improve with refraction. Relative afferent pupillary defect was negative, but pupillary light reflex was sluggish in both eyes. On slit-lamp examination, there was moderate PSC cataract and mild anterior vitreous cells. IOP was normal without using anti-glaucoma medications. Fundus examination revealed severe waxy optic disk pallor with 0.3 vertical cup-to-disk ratio and sharp margins. Severe vascular attenuation and diffuse bone spicule pigmentation were observed in all quadrants.

A point mutation in exon 2 of *RHO* gene (c.530 G > A) was detected in the proband, resulting in arginine to lysine change at amino acid position 177 (p.R177K) which was located within the transmembrane portion. (GenBank accession number: KJ849294). The other affected individuals of this family were not available for segregation analysis. Therefore, investigation of this variant was carried out in multiple unaffected family members (individuals 3:2, 4:1, 4:2 and 4:3) showing no similar variant.

Family 5

The proband was a 51-year-old woman (Fig. 1E, individual 3:10) with nyctalopia from childhood. The visual acuity was 20/25 without any refractive errors in both eyes. He had mild PSC cataract and anterior vitreous cells as well as retinal findings of typical RP. Pedigree is shown in Fig. 1-E.

A novel variant was found in exon 4 of *RHO* gene (c.930 C > G) leading to substitution of asparagine by lysine in amino acid position 310 (p.N310K) at cytoplasmic portion of rhodopsin (GenBank accession number: KP718610). The other affected individuals of this family were not available for segregation analysis. Therefore, investigation of this variant was carried out in multiple unaffected family members (individuals 3:2, 4:1, 4:2 and 4:3) showing no similar variant.

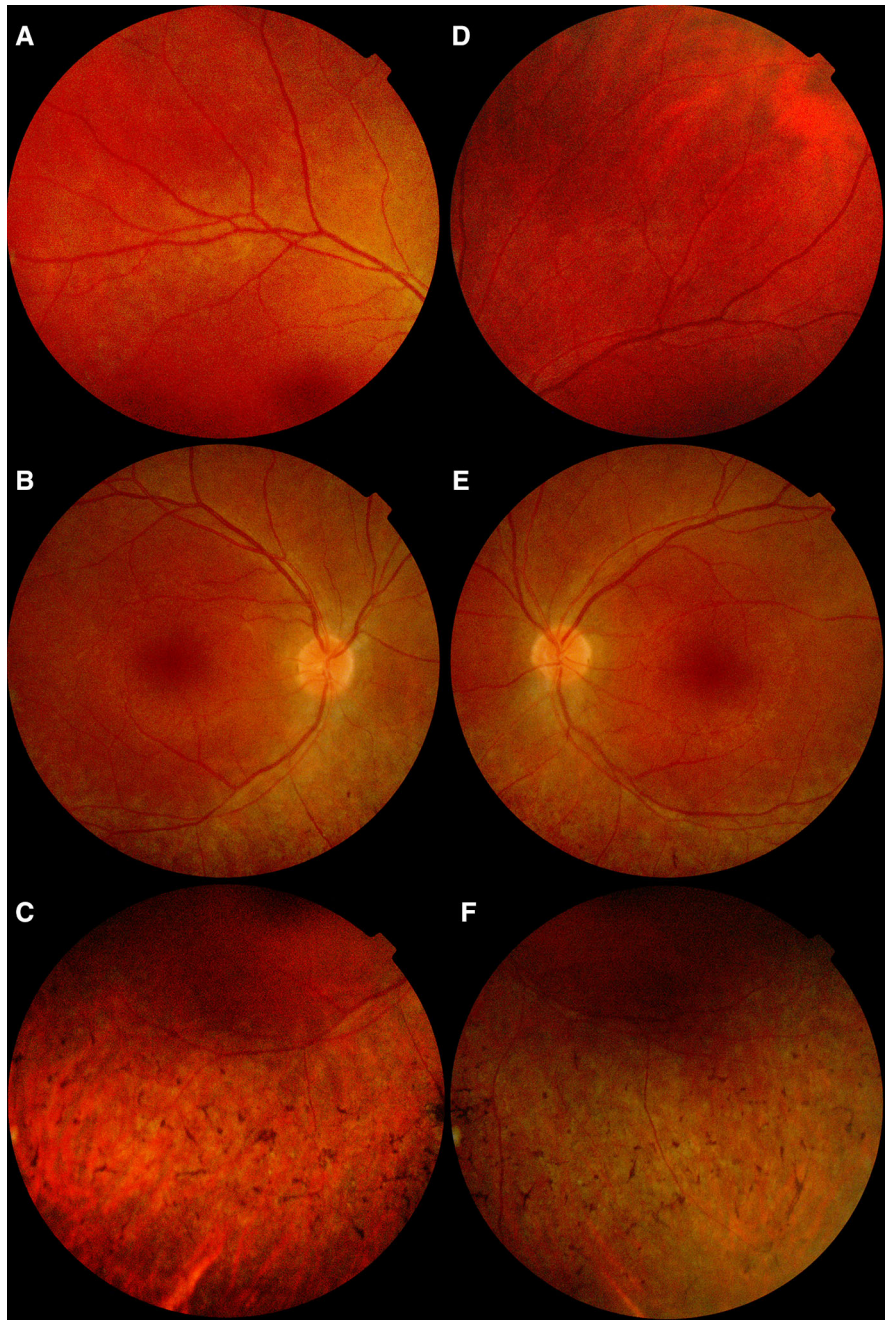

Fig. 2 Fundus photograph of the right (A–C) and left eye (D–F) of the patient with p.L95P mutation (Family 3). Retinal changes are more predominant in the inferior retina

Discussion

This study reports the genetic investigation of *RHO* gene in Iranian patients with autosomal dominant retinitis pigmentosa. Direct sequencing of the coding regions of the *RHO* gene revealed one previously reported mutation and 3 novel variants in, respectively, 2 and 3 ADRP unrelated families (23.8%). We also found a possible genotype–phenotype correlation, which remains to be confirmed by future functional studies.

In a study carried out on 68 Japanese patients with RP, Ando and colleagues found no disease-causing mutation in *RHO* gene [3]. Conversely, Sullivan and

Table 3 Clinical characteristics of patients with *RHO* gene mutation

Family no.	Detected variant	Mutation taster	CONDEL	PROVEAN	SIFT	PPH2	MA	M-CAP	FATHMM	EXAC	Iran Variome
Family 3	p.L95P	Disease causing	Neutral (0.51738)	Deleterious	0	0.955	2.74	Possibly Pathogenic	1.46	0	0
Family 4	p.R177K	Disease causing	Deleterious (0.60539)	Neutral	0	0.996	3.375	NA	1.19	0.000008	0
Family 5	p.N310K	Disease causing	Deleterious (0.59303)	Deleterious	0	1	2.975	Possibly Pathogenic	0.76	0	0

MT mutation taster, *CONDEL* CONsensus DELeteriousness score of non-synonymous single nucleotide variants (SNVs), *PROVEAN* protein variation effect analyzer, *SIFT* sorting intolerant from tolerant, *PPH2* PolyPhen-2, *MA* mutation assessor, *M-CAP* Mendelian clinically applicable pathogenicity, *FATHMM* functional analysis through hidden Markov models, *EXAC* exome aggregation consortium, *NA* not available

colleagues reported a prevalence of more than 26% among ADRP patients in the USA [7]. The prevalence of Rhodopsin gene mutations in French, Spanish and Italian ADRP patients was 16%, 8–21% and 16%, respectively [6, 8, 15, 16]. Inglehearn and colleagues detected *RHO* mutations in 10 of 20 (50%) of ADRP families by direct sequencing [17]. Development of the newer technologies, including targeted next-generation sequencing and whole exome sequencing which allow massive screening of all ADRP-associated genes, has significantly increased detection rate of sequencing methods [18].

This wide-range diversity might be due to differences in criteria for diagnosis of the disease or determination of inheritance pattern. Furthermore, higher prevalence in American population might be at least partly due to the presence of P23H mutation which is specific to this population and accounts for about 10% of cases [7]. We excluded patients with atypical history and/or clinical presentation and included patients with definite autosomal dominant inheritance.

Similar to previous reports, p.P347L was the most frequent non-P23H mutation in our study accounting for about 10% of cases [4, 6, 8]. This mutation is located on the terminal part of the coding region of the *RHO* gene and is classified as group 1 mutations in Mendes classification [12]. There are reports that p.P347L mutation may be associated with severe form of the disease [19]. However, in our study, both patients with this mutation had good visual acuity after 34 and 17 years of the disease onset (Table 2).

We also detected three novel variants in *RHO* gene in the studied population. We could not perform comprehensive segregation analysis because the blood samples of the affected relatives were not available, but mutation analysis of two of these novel variants (p.R177K and p.N310K) in unaffected family members showed that none of them had such variants. However, the p.L95P variant was observed in the proband's unaffected brother in family 3 who had no clinical evidence of RP. Although this finding is in favor of uncertain clinical significance of this variant, it does not rule out its pathogenicity. There are reports of the late-onset cases of the ADRP in which the clinical and electrophysiological manifestations may become evident in the fourth decade of life [20].

As shown in Table 2, the 3 novel variants have been classified as "variants of unknown clinical significance" according to the American College of Medical Genetics and Genomics (ACMGG) guideline which shows the lack of strong evidence supporting their pathogenicity [21]. We used multiple tools to evaluate functional consequence of the novel mutations which showed pathogenicity of all of the novel mutations with high specify and sensitivity. Since this mutation was observed in a relative without typical symptoms and signs of RP, these results should be interpreted carefully. Hence, slight RPE changes in this apparently normal relative might be a sign of early disease which might become symptomatic in the future.

We identified a characteristic fundus appearance with predominantly inferior retinal involvement in one of our patients who had the novel p.L95P mutation in his *RHO* gene (Fig. 2). This pattern has been described by other authors and has been attributed to more susceptibility of the inferior retina to the light-induced damage [22]. Aleman and colleagues have found that this pattern is correlated with group 2 mutations of Mendes classification which also includes p.P23H mutation [14]. Our findings suggest that the new p.L95P mutation may be classified as group 2 mutations, though it should be confirmed by molecular studies. We could not find further clinical differences between patients with and without *RHO* gene mutations.

Visual acuity was not significantly different in patients with or without *RHO* mutation (Table 2). However, severe visual loss was not observed in patients having *RHO* mutations, except in 1 patient with novel p.R177K mutation who had bilateral optic atrophy due to multiple attacks of optic neuritis in the setting of multiple sclerosis. This may reflect better overall visual prognosis in patients who have mutation in their *RHO* gene. Although there are reports that p.P347L mutation is associated with poorer visual prognosis [19], both of our patients with this mutation had visual acuity higher than or equal to 20/70 in both eyes (Table 2).

While this study has detected the underlying mutation in 23.8% of ADRP patients by covering only one gene, even newly conducted studies using whole exome sequencing have been reported to fail the detection of the causative mutation in about 60% of the patients with ADRP [18]. However, targeted next-generation sequencing encompassing a large number of RP-associated genes in a highly selected population

like our cohort of patients would lead to a higher diagnostic yield. Such approach is suggested to uncover the mutations in the remaining families with undetected mutations.

Compliance with ethical standards

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

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