

# Characterization of *PROM1* p.Arg373Cys Variant in a Cohort of Chinese Patients: Macular Dystrophy Plus Peripheral Bone-Spicule Degeneration

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Received: November 16, 2020

Accepted: April 21, 2021

Published: May 18, 2021

Citation: Wang Y, Wang P, Li S, et al. Characterization of *PROM1* p.Arg373Cys variant in a cohort of Chinese patients: Macular dystrophy plus peripheral bone-spicule degeneration. *Invest Ophthalmol Vis Sci*. 2021;62(6):19. <https://doi.org/10.1167/iovs.62.6.19>

**PURPOSE.** The *PROM1* p.Arg373Cys variant has been reported to cause dominant Stargardt disease, cone-rod dystrophy, and occasionally retinitis pigmentosa. This study aimed to evaluate the common phenotype associated with this variant in Chinese patients.

**METHODS.** Variants in *PROM1* were collected from in-house exome data. Potential pathogenic variants were selected, verified, and then confirmed by Sanger sequencing and co-segregation analysis. Ocular phenotypes were reviewed and further clarified by ophthalmologic examinations.

**RESULTS.** The heterozygous c.1117C>T (p.Arg373Cys) variant was identified in four unrelated families, and biallelic variants were detected in three families. Of the 10 patients from four families with the p.Arg373Cys variant, six patients from three families who underwent full fundus examination demonstrated various degrees of macular dystrophy, as well as typical bone-spicule pigment deposits in the peripheral retina. The remaining four patients did not undergo a full dilated fundus examination. A relatively preserved zone was observed between the macular and peripheral lesions. Electroretinography results showed cone and rod involvement in three patients.

**CONCLUSIONS.** Unlike Stargardt disease alone, which was considered to be the main phenotype of the p.Arg373Cys variant, all patients with full-field fundus examination in our study presented with macular dystrophy plus peripheral retinopathy resembling retinitis pigmentosa. Different phenotypes associated with the p.Arg373Cys variant may actually reflect different stages of the same disease: a predominant central cone phenotype at an early stage and peripheral rod involvement as degeneration progresses. Evaluation of the full fundus, especially the peripheral region in additional patients, is expected to confirm our findings.

Keywords: *PROM1*, p.Arg373Cys variant, bone-spicule degeneration, macular dystrophy

The Prominin 1 (*PROM1*; HGNC: 9454; OMIM: 604365) gene is located at 4p15.32 and encodes an 865-amino-acid glycoprotein containing five transmembrane domains.<sup>1</sup> The protein product of *PROM1*, mainly localized at the bases of the outer segments in rods and cones, is involved in the normal morphogenesis of the photoreceptor disk membrane and plays a critical role in autophagy of the retinal pigment epithelium.<sup>2,3</sup> Biallelic variants in *PROM1* have been reported to cause autosomal-recessive rod-dominant diseases: retinitis pigmentosa 41 (RP41, OMIM: 612095)<sup>4-6</sup> and occasionally cone-rod dystrophy 12 (CORD12; OMIM: 612657).<sup>3,7,8</sup> The most common autosomal dominant variant in this gene, c.1117C>T (p.Arg373Cys), has thus far been reported to mainly cause autosomal-dominant cone-dominant diseases: Stargardt disease 4 (STGD4; OMIM: 603786),<sup>3,9-13</sup> retinal macular dystrophy 2 (MCDR2; OMIM: 608051),<sup>3,11,14,15</sup> and CORD12.<sup>3</sup> In addition, two families with the p.Arg373Cys variant were diagnosed with retinitis pigmentosa.<sup>11,16</sup> It might be interesting to determine why the same variant results in different

phenotypes. Moreover, four novel heterozygous variants: c.2485G>A (p.Asp829Asn),<sup>17</sup> c.734T>C (p.Leu245Pro),<sup>18</sup> c.334T>C (p.Cys112Arg), and c.158G>A (p.Gly53Asp),<sup>10</sup> have recently been reported to cause *PROM1*-associated autosomal dominant retinal degeneration.

In the present study, variants in *PROM1* were collected from in-house exome data, and potential pathogenic variants were selected based on in silico online prediction tools and associated phenotypes with reference to previously established evidence. The heterozygous presence of the c.1117C>T (p.Arg373Cys) variant was identified in four unrelated families, and biallelic variants were detected in three families. Several common disease-specific features, including various degrees of macular dystrophy in the central macula, typical bone-spicule pigment deposits in the peripheral retina, and a relatively preserved mid-retina between those regions, were identified in Chinese patients with the p.Arg373Cys variant. The phenotypes of our patients at different ages and a systematic evaluation of previously published data indicated that different

phenotypes associated with the *PROM1* p.Arg373Cys variant may actually be age-dependent changes in the same disease. The disease associated with the p.Arg373Cys variant may actually present a mild cone-predominant phenotype in the early stage, followed by rod involvement in a later stage.<sup>19</sup>

## METHODS

### Probands and Family Members

This study was approved by the institutional review board of the Zhongshan Ophthalmic Centre. The probands were patients with various forms of genetic eye conditions, and their accessible family members were recruited from our Paediatric and Genetic Clinic Department, Zhongshan Ophthalmic Centre, Guangzhou, China. Written informed consent consistent with the tenets of the Declaration of Helsinki was acquired from the probands or their guardians before the clinical records and venous blood samples were collected. Genomic DNA was prepared from leukocytes obtained from venous blood using a method described previously.<sup>20</sup>

### *PROM1* Variant Detection and Identification

Variants in *PROM1* were collected from our in-house exome sequencing data on 7092 probands with different eye conditions, including 5307 probands who had undergone whole-exome sequencing and 1785 probands who had undergone targeted exome sequencing. The procedures used to perform whole-exome sequencing and targeted exome sequencing have been described in our previous study.<sup>21</sup> These probands has been diagnosed with variable ocular disease, including 1019 with retinitis pigmentosa, 1217 with glaucoma, 1299 with high myopia, 492 normal controls, and 3065 with other ocular conditions. The variants were primarily filtered by multistep bioinformatics analyses, according to the procedures described in our previous studies.<sup>21</sup> Variants with low coverage depth of reads ( $\leq 5$ ) and variants located in non-coding regions with no effect on splicing were excluded from further analysis. Variants with minor allele frequencies greater than 0.01 as recorded in existing online databases, including 1000 Genomes (<http://phase1browser.1000genomes.org/>) and gnomAD (<http://gnomad.broadinstitute.org/>), were excluded, as well. The pathogenicity of missense variants was predicted through five in silico online tools, including SIFT (<http://sift.jcvi.org/www/SIFT.enstsubmit.html>),<sup>22</sup> PolyPhen-2 (<http://genetics.bwh.harvard.edu/pph2/index.shtml>),<sup>23</sup> PROVEAN ([https://provean.jcvi.org/genome\\_submit\\_2/](https://provean.jcvi.org/genome_submit_2/)), REVEL (<https://sites.google.com/site/revelgenomics/>),<sup>24</sup> and CADD (<https://cadd.gs.washington.edu/>).<sup>25</sup> The prediction scores assigned to the missense variants by Rare Exome Variant Ensemble Learner (REVEL) and Combined Annotation-Dependent Depletion (CADD) were evaluated by comparison with the 75% and 95% cut-off scores calculated from gnomAD data. The potential influence on splicing of intronic variants was predicted based on the Berkeley Drosophila Genome Project (BDGP; <http://www.fruitfly.org/>).<sup>26</sup> Data from the Human Genome Mutation Database (HGMD; <http://www.hgmd.cf.ac.uk/ac/index.php>) were used to evaluate potential pathogenic variants. *PROM1* variants were confirmed by Sanger dideoxy sequencing as described previously,<sup>27</sup> followed by further co-segregation analysis and genotype-phenotype analysis in available families.

## Phenotypic Characterization

The clinical records of patients with the *PROM1* p.Arg373Cys variant or with biallelic variants were reviewed and evaluated. Ophthalmologic examinations were performed if possible, including best-corrected visual acuity, refractive error, axial length, fundus photography, scanning laser ophthalmoscopy, fundus fluorescein angiography (FFA), fundus autofluorescence (FAF), and electroretinogram (ERG). Autofluorescence was excited with a 488-nm argon laser, and FAF images were visualized through a 500-nm longpass barrier filter to block short wavelengths. ERGs were recorded by using a Roland RETI-port (Roland Consult, Brandenburg, Germany) or Espion Ophthalmic Electrophysiology System (Diagnosys, Lowell, MA, USA) in a dark room according to the international standards of the International Society for Clinical Electrophysiology of Vision.

### Mini-Review of *PROM1* p.Arg373Cys Variant in Literature

Previously published literature regarding the heterozygous p.Arg373Cys variant of *PROM1* was reviewed, and the clinical data of the patients with the p.Arg373Cys variant in these published studies were summarized.

## RESULTS

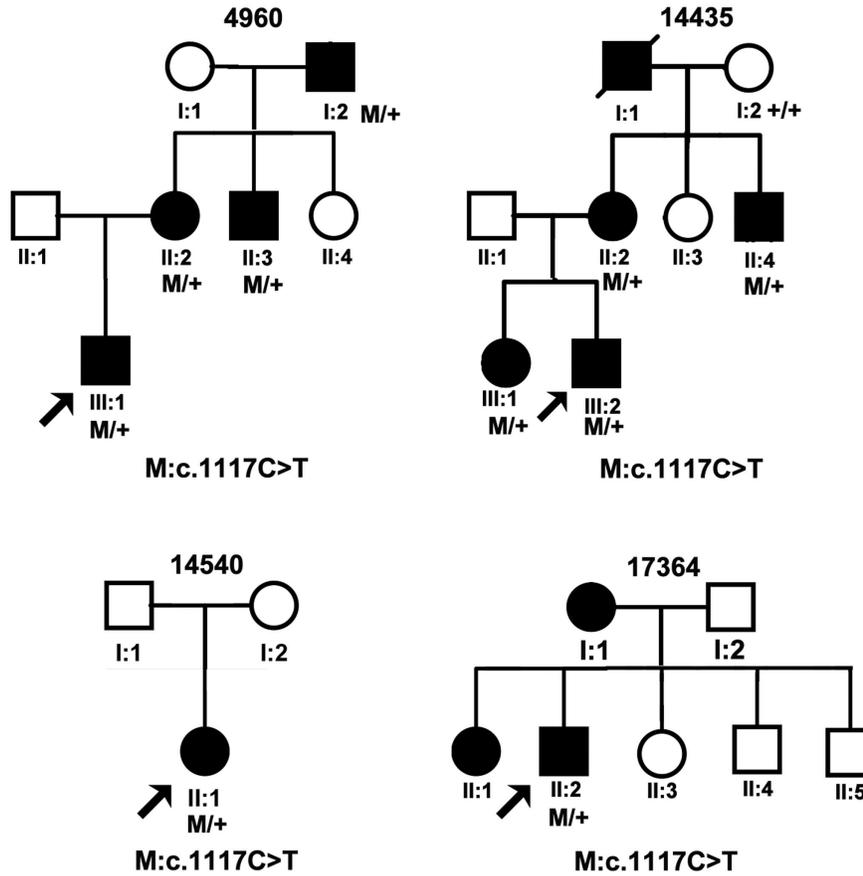
### *PROM1* Potential Pathogenic Variants Identified in Seven Chinese Families

Four potential pathogenic variants in *PROM1* were detected in seven families, including four families with heterozygous variant and three families with biallelic variants. These variants were two truncation variants (c.139delC/p.His47Ilefs\*12 and c.2226T>G/p.Tyr742\*) and two missense variants (c.1415G>A/p.Arg472Gln and c.1117C>T/p.Arg373Cys), of which two were novel and absent from the gnomAD database (Supplementary File S1). Both of the missense variants were predicted to be damaging by at least four online in silico prediction tools. The homozygous c.139delC/p.His47Ilefs\*12 variant was detected in two probands, whereas variant c.2226T>G/p.Tyr742\* and variant c.1415G>A/p.Arg472Gln were detected in one proband. The heterozygous c.1117C>T/p.Arg373Cys variant was identified in 10 patients from four families. Co-segregation analysis in available family members confirmed the pathogenicity of the p.Arg373Cys variant (Fig. 1; Supplementary Fig. S1). The other four recently published heterozygous variants and novel potentially pathogenic heterozygous variants were not identified in our study.

### Phenotypic Features of Patients With *PROM1* Variants

The heterozygous p.Arg373Cys variant was segregated with different forms of retinal degeneration in 10 patients from four families (Table). The age of onset ranged from childhood to 50 years, and onset occurred before 5 years of age in four patients. All patients had an ocular complaint of poor vision at the beginning of disease; five of them had night blindness, and four had difficulty distinguishing colors. Best-corrected visual acuity ranged from 0.03 to 0.60, except for one eye with no light perception due to trauma-associated retinal detachment.

### Families with the heterozygous variant p.Arg373Cys



**FIGURE 1.** The pedigrees of four families with the heterozygous p.Arg373Cys variant in *PROM1*. Squares indicate males, circles indicate females, and shading indicates an affected individual. Probands are indicated by arrows. Sample numbers are shown above the pedigrees, and variants are listed below the pedigrees.

**TABLE.** Clinical Information for Four Families With Heterozygous p.Arg373Cys Variant in *PROM1*

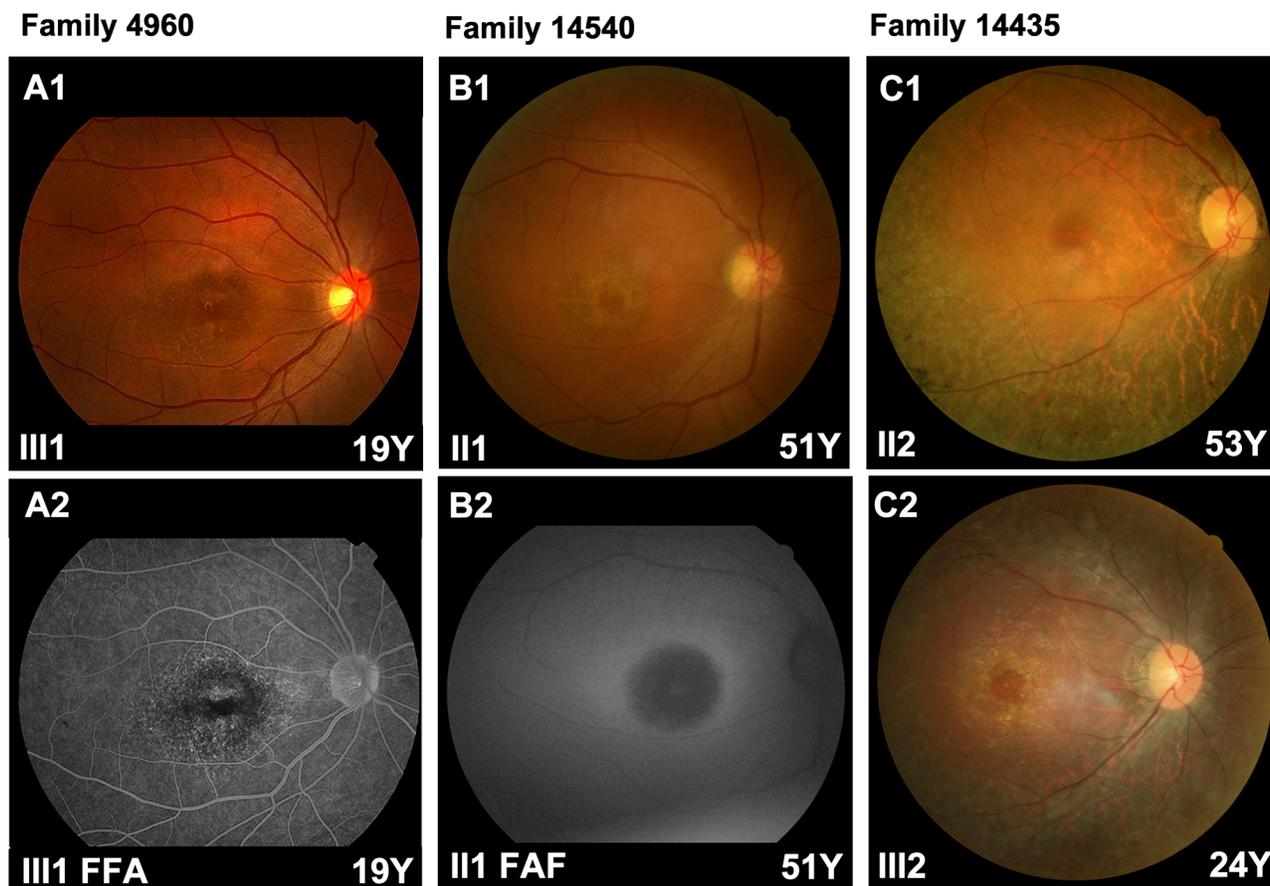
DNA ID	Gender	Age (y) at		AL or Refraction	First Symptom	Visual Acuity		Fundus		ERG	
		Onset	1st Exam			OD	OS	OD	OS	Rods	Cones
4960-I2	M	23.0	75.0	NA	PV, CB	0.03	NLP*	NA	NA	NA	NA
4960-II2	F	23.0	49.0	NA	PV, CB	0.30	0.10	MD	MD	NA	NA
4960-II3	M	4.0	45.0	+0.50/+0.75	PV, CB	0.10	0.05	MD, PPD	MD, PPD	UN	UN
4960-III1	M	EC	19.0	NA	PV, CB	0.60	0.30	MD	MD	NA	NA
14435-II2	F	50.0	53.0	NA	PV, NB	NA	NA	MD, PPD	MD, PPD	NA	NA
14435-II4	M	30.0	47.0	NA	PV, NB	0.40	0.30	MD, PPD	MD, PPD	NA	NA
14435-III1	F	NA	30.0	-4.75/-3.75	PV, NB	NA	NA	MD, PPD	MD, PPD	NA	NA
14435-III2	M	EC	24.0	+0.25/+0.25	PV, NB	0.20	0.20	MD, PPD	MD, PPD	UN	UN
14540-III1	F	EC	39.0	-2.25/-3.25	PV, NB	0.12	0.12	MD, PPD	MD, PPD	MR	SR
17364-II2	M	16.0	43.0	NA	PV	0.15	0.15	MD	MD	NA	NA

ID, identification; AL, axial length; ERG, electroretinogram; M, male; F, female; NA, not available; PV, poor vision; CB, color blindness; NLP, no light perception; MD, macular dystrophy; PPD, peripheral pigment deposits; UN, undetectable; EC, early childhood; NB, night blindness; MR, moderately reduced; SR, severely reduced.

\* This eye was blind due to trauma-associated retinal detachment.

Detailed ophthalmic evaluations were available in six patients of three families, whereas the remaining four patients, including three individuals from family 4960 and

proband 17364-II2, did not undergo full-field fundus examinations. All six of these individuals from three families showed various degrees of macular dystrophy. Proband



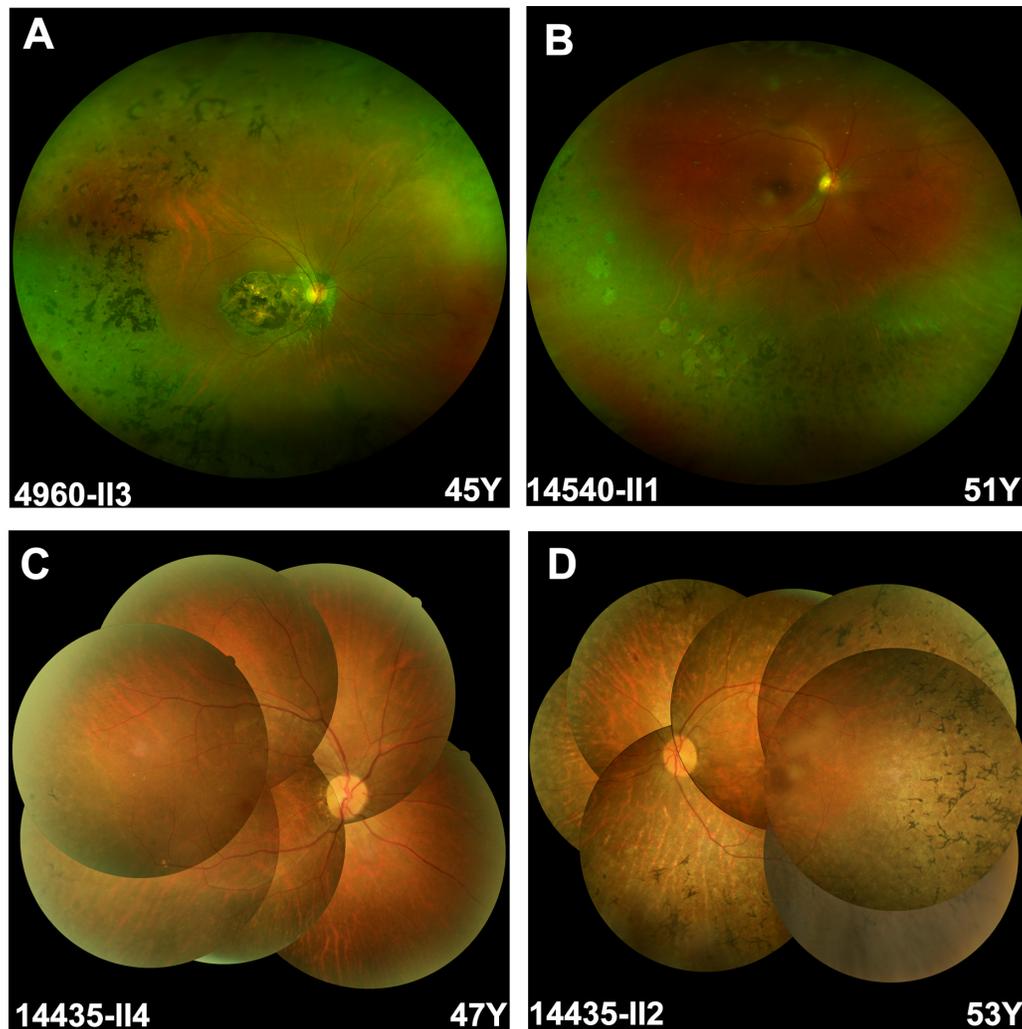
**FIGURE 2.** Fundus photography, FFA, and FAF imaging of the patients with the heterozygous p.Arg373Cys variant in this study. (**A1, A2**) Patient 4960-III1 showed macular dystrophy at the central posterior pole image and presented bull's-eye hyperfluorescence around the fovea on FFA imaging. (**B1, B2**) Patient 14540-II1 had severe macular dystrophy at the posterior retina and showed a central hypofluorescent macular area surrounded by a hyperfluorescent ring on FAF imaging. (**C1, C2**) Fundus photography of two patients (14435-II2 and 14435-III2) from the same family; bone-spicule pigment deposits and macular dystrophy could be observed in the 53-year-old patient (14435-II2).

4960-III1 showed macular dystrophy on imaging of the central posterior pole and presented bull's-eye hyperfluorescence around the fovea on FFA at his first visit to our clinic (Figs. 2A1, 2A2). Peripheral bone-spicule pigment deposits plus macular dystrophy were observed at follow-up for individual 4960-II3 (Fig. 3A). Proband 14540-II1, with a sporadic case, had severe macular dystrophy at the posterior retina and a central hypofluorescent macular area surrounded by a hyperfluorescent ring on FAF (Figs. 2B1, 2B2). A pigmentary change was also found at her follow-up visit (Fig. 3B). Fundus photography of two patients from the same family, 14435, showed typical macular dystrophy, as well, although severe macular dystrophy with bone-spicule pigment deposits could be observed in the central posterior pole image of the 53-year-old individual (14435-II2) in this family (Figs. 2C1, 2C2). There was a variety of peripheral pigmentary changes in four affected patients from the same family (14435), with the oldest individual (14435-II2), who was 53 years old, presenting more obvious and severe bone-spicule pigmentation than the 47-year-old family member (14435-II4) (Figs. 3C, 3D). Interestingly, a relatively preserved zone in the mid-retina was observed between the macula and the peripheral retina in all six individuals. ERG recordings were available for three patients from the three different families. Scotopic responses, 30-Hz flicker responses, and photopic responses were unrecord-

able in patients 14435-III2 and 4960-II2. Scotopic responses and 30-Hz flicker responses were moderately attenuated, and photopic responses were severely decreased in patient 14450-II1 (Fig. 4; Supplementary Fig. S2). Moreover, three probands with biallelic variants in *PROM1* presented typical retinitis pigmentosa phenotypes (Supplementary File S1).

### Phenotypes of the p.Arg373Cys Variant in the Literature

Twenty-eight families in total have been reported to carry the p.Arg373Cys variant. The clinical data of families with the p.Arg373Cys variant have been summarized in Supplementary Table S1. This variant was reported in various ethnicities, including Chinese, Caribbean, Italian, British, and African American, among others. The age at onset ranged from childhood to 58 years, with the first symptoms being reduced central vision and photophobia. The 28 families included three families with cone-rod dystrophy, 19 with Stargardt disease, two with retinal macular dystrophy, two with bull's eye maculopathy, and two with retinitis pigmentosa. According to the available clinical data, all of these patients had macular lesions, including six families of patients presenting bull's eye maculopathy, five families



**FIGURE 3.** Full-field fundus examination and scanning laser ophthalmoscopy results of the patients with the p.Arg373Cys variant in this study. Characteristic macular involvement and peripheral pigment deposits separated by a relatively preserved mid were observed in the patients with the heterozygous p.Arg373Cys variant in *PROM1*.

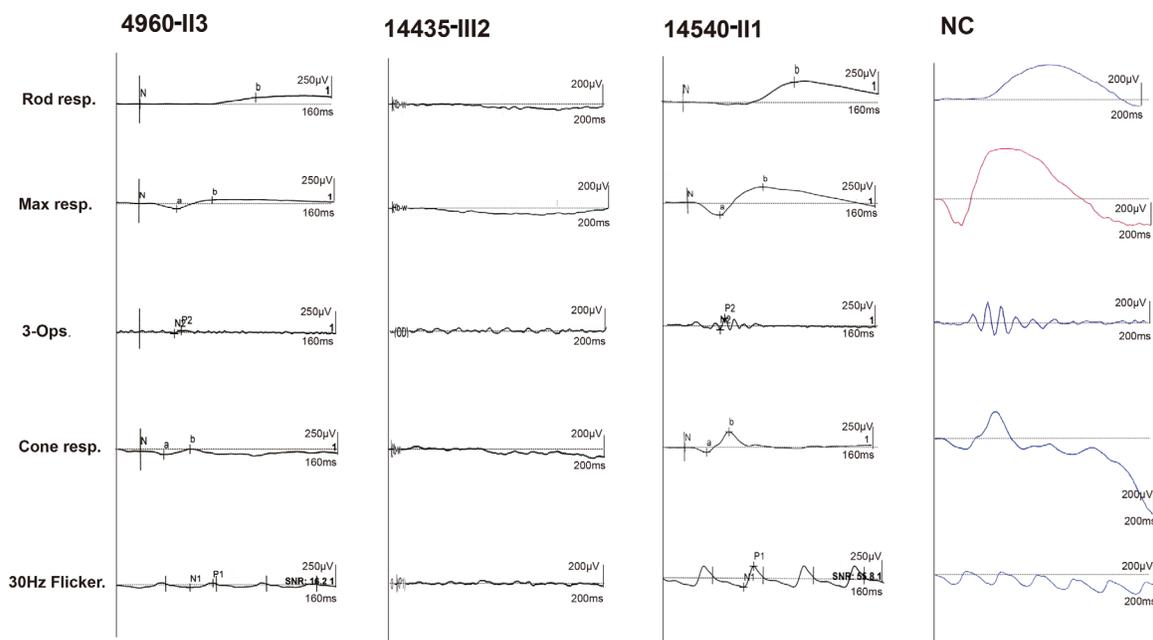
with pigmentation in the macular area, and two families that showed flavimaculatus flecks. Peripheral pigment deposits were found in two families of Italian and Spanish ethnicity.

## DISCUSSION

In this study, all participants who underwent the exome sequencing presented different eye conditions that were not limited to the phenotype resembling retinitis pigmentosa. Based on our in-house data, the variants in *PROM1* were selected and filtered by multistep bioinformatic analysis and co-segregation analysis. Two novel recessive variants, c.1415G>A/p.Arg472Gln and c.2226T>G/p.Tyr742\*, were identified, expanding the spectrum of variants associated with *PROM1*. The well-known heterozygous p.Arg373Cys variant of *PROM1* was identified in 10 individuals from four unrelated families with autosomal dominant retinal degeneration. Overall, the potential sources of ascertainment bias were minimized as much as possible in this study. The detailed widefield fundus examination, which was performed in four patients from a large family and two follow-up patients from the other two families

with the p.Arg373Cys variant, revealed a common phenotype: severe macular involvement with peripheral pigment deposits.

The characteristics of the fundus changes observed in the current study may be of help in explaining the various forms of retinal degeneration associated with the p.Arg373Cys variant, such as Stargardt-like macular dystrophy with yellowish flecks,<sup>3,9</sup> specific bull's eye retinal pigment epithelium dystrophy with central fovea sparing,<sup>3,11,14</sup> and occasionally severe macular dystrophy accompanied by possible pigmentation changes in the peripheral retina.<sup>11,16</sup> Characteristic macular involvement was found in all previously reported patients of 28 families with the p.Arg373Cys variant,<sup>3,9-16,19,28</sup> which might overlap with cone-rod dystrophy and progression to rod-cone like dystrophy over time.<sup>29</sup> In addition, severe macular dystrophy, bull's eye fundus changes, and cone-rod dystrophy associated with the p.Arg373Cys variant may actually be present in the same eye, between two eyes of the same patient, or among different affected individuals in the same family if they are examined by different methods (with or without ERG or FFA) at different times or by different people.



**FIGURE 4.** The ERG examination results of three patients with the heterozygous *PROM1* p.Arg373Cys variant in this study. Scotopic responses and 30-Hz flicker responses were unrecordable in patient 14435-III2, severely reduced in patient 4960-II2, and moderately attenuated in 14450-III1. Photopic responses were also unrecordable in one patient (14435-III2) and severely decreased in patients 4960-II2 and 14450-III1.

Peripheral bone-spicule pigment deposits along with macular dystrophy fundus changes have been reported in two large Caucasian case series.<sup>11,16</sup> However, one reported Chinese family and eight Japanese families that were identified as having the p.Arg373Cys variant presented only macular atrophy fundus changes, with no mention of retinal peripheral pigment deposits.<sup>10,13</sup> In the current study, in all six affected individuals with the p.Arg373Cys variant who underwent detailed widefield fundus examination, peripheral bone-spicule appearance degeneration was seen, in addition to macular lesions, suggesting that changes resembling retinitis pigmentosa are not an ethnically specific phenotype. In our opinion, typical bone-spicule pigmentation in the peripheral retina may be rarely observed in routine clinical practice, as it is slightly far from the mid-retina. In such circumstances, therefore, macular change may dominate the diagnosis if specific peripheral retinal degeneration is not detected. The application of widefield fundus examination should be emphasized among patients with the particular variant, and further studies are expected to reveal whether macular dystrophy plus peripheral pigment deposits is a common phenotype of the variant.

A limitation of this study was that widefield autofluorescence examination, which could display the obvious preserved region of the retina, was not available in patients with the p.Arg373Cys variant. Although all six affected individuals with the p.Arg373Cys variant presented the phenotype delineated in our study, one of the four families and three family members in a large family did not undergo detailed full-field fundus examination due to loss of follow-up. The heterogeneity among different families or different individuals from the same family should be considered when analyzing the phenotype of the particular variant. However, there was not enough evidence to illuminate family heterogeneity from the clinical manifestation based on our study's

findings. Further studies on the peripheral retinal region of patients with the p.Arg373Cys variant are needed to reveal the familial heterogeneity.

Moreover, such variety in the clinical manifestations of the p.Arg373Cys variant may actually reflect different stages of the disease. It has recently been reported that the phenotype associated with *PROM1* was actually cone-rod dystrophy not only in the recessive inheritance mode but also in the dominant mode. In contrast to the recessive variants associated with severe peripheral retinal degeneration, the dominant missense p.Arg373Cys variant in *PROM1* was associated with a milder predominant central cone phenotype.<sup>19</sup> In this case series study, the ERG results of three individuals with the heterozygous variant revealed that the phenotype associated with the p.Arg373Cys variant was manifested as peripheral rod involvement and was consistent with fundus pigmentary changes. Additionally, peripheral pigment deposits were more obvious in the oldest patients than in the younger affected individuals from the same family. It is hypothesized that peripheral pigmentary changes may not be obvious in the early stage of the disease and are usually observed in the late stage. We are eager to test this hypothesis through follow-up studies of the individuals with the variant. Inherited retinal dystrophy is a leading cause of blindness worldwide, and careful description of multiple families with these specific variants is necessary to enhance our understanding of the disease. The possible specific phenotype associated with the most common heterozygous variant delineated in our study enriches the genotype-phenotype correlations of the *PROM1* gene, refines clinical diagnostics, and guides possible future gene therapy.

Unlike the recessive variants in *PROM1*, which exert a loss-of-function effect and lead to the absence of the protein,<sup>30</sup> the dominant p.Arg373Cys variant may be associated with a milder phenotype due to a dominant

negative effect of the missense variant.<sup>19</sup> Currently, lentivirus-based therapy has been used for *ABCA4*-associated Stargardt disease,<sup>31</sup> and gene replacement and augmentation therapy using subretinal injections of adeno-associated virus vectors has been applied in *RPE65*-associated dystrophies.<sup>32</sup> Subretinal delivery of adeno-associated viral vector treatment was applied in the recessive *PROM1* variants associated with retinal degeneration and rescued the phenotype at an early stage.<sup>19</sup> For the gain-of-function dominant variants in *PROM1*, a gene-editing therapy such as the CRISPR/Cas9 system is expected to address these variants soon.

## CONCLUSIONS

A common phenotype of Chinese patients with the *PROM1* variant p.Arg373Cys was identified: severe macular involvement with peripheral bone-spicule degeneration. Overall evaluation of our data together with previously published data suggests that some of the various phenotypes associated with this variant might be related to different stages of the same disease, but it is also possible that different populations manifest different phenotypes. We highlight the importance of reporting changes in the peripheral retina that can go unnoticed. It will be interesting to assess whether these findings are replicated in future studies.

## Acknowledgments

Supported by Grants from National Natural Science Foundation of China (81970837) and the Fundamental Research Funds of the State Key Laboratory of Ophthalmology.

Disclosure: **Y. Wang**, None; **P. Wang**, None; **S. Li**, None; **J. Ouyang**, None; **X. Jia**, None; **X. Xiao**, None; **J. Yang**, None; **X. Li**, None; **W. Sun**, None; **Q. Zhang**, None

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