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Clinical Characteristics of High Myopia in Female Carriers of Pathogenic *RPGR* Mutations: A Case Series and Review of the Literature

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Abstract

Background: *RPGR* mutations are the most common cause of X-linked retinitis pigmentosa (XLRP). High myopia has been described as a very frequent feature among affected female carriers of XLRP. However, the clinical phenotype of female patients presenting with X-linked *RPGR*-related high myopia has not been well described.

Materials and Methods: Retrospective case series of four female patients with *RPGR* mutations and a diagnosis of high myopia, who presented to two academic eye centers. Clinical data, including age, family history, visual acuity, refractive error, dilated fundus exam, fundus photography, optical coherence tomography, electroretinography, and results of genetic testing, were collected.

Results: Three *RPGR* variants identified in the present study have not been previously associated with myopia in female carriers. One variant (c.2405_2406delAG, p.Glu802Glyfs*32) has been previously associated with a myopic phenotype in a female patient. Patients became symptomatic between the first and sixth decades of life. Myopia-associated tilted optic discs and posterior staphyloma were present in all patients. Two patients presented with intraretinal migration of the retinal pigment epithelium.

Conclusion: *RPGR*-related high myopia has been associated with mutations in exons 1-14 and ORF15 in heterozygous females. There is a wide range of visual function among carriers.

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Although the exact mechanism of *RPGR*-related high myopia is still unclear, continued molecular diagnosis and description of phenotypes remain a crucial step in understanding the impact of *RPGR* mutations on visual function in female XLRP carriers.

Keywords

retinitis pigmentosa; x-linked retinitis pigmentosa; XLRP; retinitis pigmentosa GTPase regulator; RPGR; female carriers; myopia

Introduction

Retinitis pigmentosa (RP) is the most common inherited retinal disease in the world, with a prevalence of approximately 1 in 4000 individuals (1). RP is a genetically heterogeneous disease for which all patterns of Mendelian inheritance are observed. Autosomal dominant (30-40% of cases), autosomal-recessive (50-60%), and X-linked (5-15%) forms account for most cases of RP, although rare instances of digenic and mitochondrial inheritance have been reported (1, 2). RP causes the gradual loss of photoreceptors, which results in profound vision loss or blindness. Clinical hallmarks of RP include night blindness in adolescence, constriction of peripheral visual fields in young adulthood, and loss of central vision in late adulthood (1, 2). Associated non-ocular disease may be present in syndromic forms of RP such as Usher syndrome and Bardet-Biedl syndrome, but in most patients, RP is non-syndromic. To date, mutations in over 65 genes have been implicated in non-syndromic RP (1-3).

Some patients with RP can be classified by family history into the autosomal dominant (adRP), autosomal recessive (arRP), or X-linked (XLRP) genetic type. However, it is estimated that over 40% of patients present as isolated or simplex cases with no family history of disease (4, 5). Clinical examination of affected patients and family members can often be revealing of inheritance pattern, as certain findings in a routine ocular examination are significantly more prevalent in different types of RP (6). For example, individuals with XLRP are more likely to have a visual acuity of 20/50 or worse by age 20-39 and a myopic refractive error of 2.00 diopters (D) or more (mean - 5.51 D), compared to individuals with adRP or arRP (6, 7). Moreover, phenotypic high myopia has been reported as a significantly aggravating factor in female carriers of Retinitis Pigmentosa GTPase Regulator (*RPGR*) gene mutations, which are estimated to cause 70-90% of all XLRP cases (8-11). A second primary causative gene, *RP2*, is mutated in 10-20% of XLRP cases (10).

The *RPGR* gene is located on the short arm of the X-chromosome, and expresses two major alternatively spliced transcripts, $RPGR^{Ex1-19}$ and $RPGR^{ORF15}$ (Figure 1) (12). $RPGR^{ORF15}$ is the predominant isoform expressed in the retina and contains exons 1-14 of $RPGR^{Ex1-19}$ in addition to a segment known as the ORF15 exon (12, 13). Particularly, $RPGR^{ORF15}$ encodes a 1152-amino-acid protein that localizes to the connecting cilia of photoreceptors, where it is believed to facilitate protein trafficking between the inner and outer segments (12-15). $RPGR^{Ex1-19}$ is constitutively expressed in a variety of tissues and encodes an 815-amino-acid protein found in the transition zone and axoneme of primary and motile cilia (12). Approximately 20% of XLRP patients have mutations in exons 1-14, and 80% have

mutations in the repetitive glutamic acid and glycine-rich sequence of exon ORF15 (12, 13, 16).

The classic model of X-linked inheritance holds that pathogenic mutations in genes on the X-chromosome produce a phenotype solely or primarily in hemizygous males, while heterozygous females usually have no disease or manifest much less severe disease than males with the same variant (17). However, a recent cohort study of 125 heterozygous female *RPGR* mutation carriers described a wide spectrum of phenotypes ranging from asymptomatic to severe retinal degeneration, demonstrating that female carriers of XLRP can also suffer from visual dysfunction (9). Specifically, myopia was observed in 73% of heterozygotes, and complete expression of the RP phenotype was observed in 23% carriers (9). Interestingly, others have reported a distinctive X-linked genotype-phenotype correlation between RP and pathological myopia characterized by the symmetrical presence of disease in both retinas of all heterozygous female carriers, suggesting that some *RPGR* variants are highly penetrant and may underlie both RP and myopia (8, 18, 19). With novel upcoming therapeutic options including gene therapy and optogenetic strategies now being explored in Phase I/II clinical trials for the treatment of XLRP, the phenotypic characterization of *RPGR* mutations in females has gained importance (20-22). Here, we report the clinical and genetic findings of four non-consanguineous and unrelated female patients with pathogenic *RPGR* variants and concomitant high myopia.

Methods

This is a case series using retrospective chart review and data collection at two academic eye centers: Byers Eye Institute at Stanford Health Care in California, United States, and Edward S. Harkness Eye Institute at Columbia Medical Center in New York, United States. Patient eligibility criteria included female gender with a diagnosis of high myopia and the presence of an *RPGR* mutation. The diagnosis of high myopia was defined as a myopic refractive error below −6.00 D or an axial eye length greater than 26.5 mm. Genetic testing in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory was performed and those with mutations in the *RPGR* gene were included in this study. Patients underwent a complete dilated ophthalmic examination by a retinal physician (V.B.M., S.H.T.), which included color fundus photography with a Fundus Camera (Carl Zeiss Meditec AG, Jena, Germany). Fundus autofluorescence (FAF) images were obtained using a confocal scanning-laser ophthalmoscope (Heidelberg Retina Angiograph, Heidelberg Engineering, Dossenheim, Germany). Simultaneous FAF and spectral domain optical coherence tomography (SD-OCT) images were acquired using Spectralis Heidelberg OCT Engineering (Heidelberg, Germany). RPGR protein structure modeling was processed by I-TASSER web server, which builds structural models starting from templates of similar proteins (23). Models were visualized with PyMOL (The PyMOL Molecular Graphics System, Version 2.5, Schrödinger, LLC). This study conformed to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Boards of all participating centers.

Results

Case 1

A 50-year-old female patient with self-reported blurred vision since childhood, did not require the use of visual aids until college age. Beginning in her mid 40s, the patient noticed marked progressive visual loss and distortion. The patient's past medical history revealed a diagnosis of open-angle glaucoma in both eyes in the last year and bilateral cataracts. Her cataract in the right eye was surgically treated by phacoemulsification with implantation of an intraocular lens. The BCVA was now 20/50 and 20/20 in the right and left eye, respectively. Refraction indicated pathological myopia with refraction of −13.00 D in the right eye. The left eye showed refraction of −11.50 D. IOP at presentation was 11 mmHg in her right eye and 12 mmHg in her left eye. Slit lamp examination showed posterior vitreous detachment. The posterior segment revealed bilateral peripapillary atrophy, severely tilted optic discs, and optic nerve rim thinning (cup/disc ratio of ~0.85), and macular coloboma with atrophic changes (Figure 2A,C). Spectral domain optical coherence tomography (SD-OCT) showed bilateral axial elongation and posterior staphyloma (Figure 2B,D). 24-2 Humphrey Visual Field (HVF) testing showed a superior arcuate defect and nasal steps in the left eye and a dense inferior arcuate defect and early superior nasal step in the right eye (Figure 2E). Genetic testing identified a deletion in ORF15 of *RPGR* (c.2706_2707delGG, p.Glu903Glyfs*175), also present in her son diagnosed with RP at a young age. This family had two asymptomatic, male and female, children (Figure 2F).

Case 2

A female patient was first seen at the age of 19 years for retinal evaluation. Over the past several years, she experienced poor night vision and difficulty negotiating in dark places, but denied trouble with peripheral or color vision. ERG showed essentially no rod function and significantly reduced cone function. She had a strong family history for RP that was most consistent with the autosomal dominant subtype. Her father, uncle, and paternal grandmother were known to be affected with RP. Her BCVA at the time was 20/40 in both eyes. She was examined again at 30 years of age. The BCVA at her most recent visit was 20/100 in the right eye and 20/70 in the left eye. IOP was 17 mmHg and 16 mmHg in the right and left eye, respectively. Her anterior eye examination was unremarkable. Fundus examination showed severely attenuated vessels, tilted optic discs, and tilted optic cups in both eyes. In the periphery of both eyes, bone-spicule shaped pigment deposits anterior to the arcades were observed. In the macula of both eyes, a myopic contour, posterior staphyloma, and severe outer retinal loss with a central island was observed by means of SD-OCT (Figure 3A,B). Goldmann visual field (GVF) testing showed markedly constricted visual fields to a diameter of 30 degrees to a V-4-e target and a diameter of 10 degrees to an I-4-e target in the right eye, and a diameter of 20 degrees to a V-4-e target and a diameter of 8 degrees to an I-4-e target in the left eye. Genetic testing revealed a mutation in ORF15 of *RPGR* (c.2517_2518delAG, p.Glu841Glyfs*237).

Case 3

A 54-year-old woman was diagnosed with RP in 2010. The patient's family history included a paternal granduncle, father, and two sons who were all diagnosed with RP in the first

decade of life, in addition to a sister with high myopia (Figure 4A). Her BCVA at evaluation was 20/60 in the right eye and 20/80 in the left eye. She had pathological myopia with a current refraction of −16.00 D in the right eye and −15.25 D in the left eye. IOP measured 18 mmHg and 19 mmHg in the right and left eye, respectively, without diagnosis of glaucoma. Anterior segment exam revealed mild nuclear sclerotic cataracts bilaterally. Dilated fundus exam revealed moderate intraretinal migration of the retinal pigment epithelium (RPE) cells throughout the entire fundus with evidence of pigment in the macula of both eyes (Figure 4B,C). ERG 30 Hz-flicker recordings showed reduced responses in both eyes. Genetic testing revealed a single base-pair deletion in exon 10 of *RPGR* (c.1100delC, p.Pro367Leufs*14).

Case 4

This 80-year-old woman with a history of laser-assisted in-situ keratomileusis (LASIK) eye surgery 14 years ago, remained highly myopic in the right eye (−7.00 D). She was referred for retinal evaluation after her son was diagnosed with cone-rod dystrophy with the *RPGR* c.2405_2406delAG hemizygous mutation, located in the ORF15 exon. Genetic testing revealed the same 2-base-pair deletion (c.2405_2406delAG, p.Glu802Glyfs*32) as her son. She had no other family history of any ophthalmologic disease. Her BCVA at initial presentation was 20/40 in the right eye and 20/25 in the left eye. This patient's anterior segment examination was unremarkable; however, a tapetal-like reflex was observed along with peripapillary atrophy in both eyes during a dilated fundus exam with more atrophy in the right than the left eye (Figure 5A,B). Additionally, autofluorescence imaging showed a hyperfluorescent lesion surrounded by an area of hypofluorescence in the periphery of the right eye, with pigment migration surrounded by RPE loss (Figure 5E,F).

Discussion

XLRP is commonly caused by mutations in the *RPGR* gene on the X-chromosome. Currently, the Human Gene Mutation Database (HGMD) lists 304 unique *RPGR* mutations in the $RPGR^{ORF15}$ variant (version 2021.4, accessed February 2022) (24). Patients with XLRP associated with *RPGR* mutations lose visual acuity at an average exponential rate of 4% per year, which contributes to the development of legal blindness at a median age of 45 years (25). Females are generally considered to be unaffected carriers of XLRP with a 50% chance of passing XLRP to their sons. However, a recently published case series of over 240 female carriers of XLRP showed that nearly 50% of carriers showed a baseline abnormality in at least one psychophysical test of visual acuity, visual field, or dark adaptation in one or both eyes (26). Additionally, a retrospective cohort study of 125 female carriers of *RPGR* mutations found that the incidence of high myopia (below −6.00 D) in heterozygous females was comparable to that of hemizygous males (35% versus 38%, respectively) (9, 27). The reasons for the association between *RPGR* mutations and high myopia remain unclear, but it is useful to report the clinical findings of additional female carriers of pathogenic *RPGR* variants, as symptomatic female heterozygotes are scarce.

In our case series, we presented the phenotypes of four non-consanguineous and unrelated female carriers with different *RPGR* variants and concomitant high myopia. Out of the

four highly myopic patients described here, three harbored mutations in exon ORF15 and one patient carried a mutation in exon 10 of *RPGR*. This is in accordance with the fact that all published disease-causing *RPGR* mutations associated with XLRP reside in exons 1-14 or ORF15, implying that the $RPGR^{ORF15}$ isoform is required for normal photoreceptor function (16, 28). Similarly, other pedigrees have observed a distinctive genotype-phenotype correlation, characterized by the manifestation of symmetrical high myopia in all heterozygous female carriers of exon ORF15 mutations (18, 19, 29).

Because exon ORF15 is located at the terminal end of the $RPGR^{ORF15}$ transcript, it is hypothesized that premature termination codons in this region are less likely to result in nonsense-mediated mRNA decay, thus resulting in truncated protein products that can potentially exacerbate the loss of function or become gain-of-function to contribute to the pathogenesis of high myopia (18, 30). Furthermore, it has been observed that transgenic mice that expressed truncated forms of RPGR due to mutations in exon ORF15 experienced faster photoreceptor degeneration than *RPGR* knockout mutants, suggesting that certain *RPGR* variants can act as dominant alleles, leading to a clinically severe phenotype in female carriers (31). Interestingly, in our case series we noticed a semi-dominant pattern of inheritance in patient 2 with the (c.2517_2518delAG, p.Glu841Glyfs*237) variant, where at least three generations of male and female individuals were diagnosed with RP. This patient manifested high myopia accompanied by severe retinal and fundoscopic changes beyond those normally observed in carriers of XLRP. A separate study identified this same variant in a family diagnosed with a semi-dominant pattern of XLRP, consisting of over four generations of affected individuals, suggesting that this mutation may be associated with an X-linked dominant mode of inheritance (32).

The *RPGR* exon ORF15 repeat domain is rich in glutamic acid residues, conferring a pronounced negative charge to the region, and is predicted to be intrinsically disordered and flexible, suggesting a possible role in protein-protein interactions (Figure 6) (12). While its function and interacting partners are currently unknown, the loss of this domain may result in a change from an acidic to basic net charge and interfere with the binding of positively charged substrates (13). The properties of the ORF15-encoded domain and its involvement in the pathogenesis of human ciliopathies including RP, have been recently investigated by Rao et al., who showed that $RPGR^{ORF15}$ is post-translationally glutamylated in the Glu-Gly domain at the photoreceptor cilium (33). The authors propose that glutamylated $RPGR^{ORF15}$ may alter the function of RPGR by modulating its ability to regulate ciliary protein trafficking (33). The variation in fundus appearance of Patients 1, 2, and 4, who each harbored mutations in ORF15, suggest that there is phenotypic variability amongst female patients with *RPGR* mutations. However, in general, exon ORF15 mutations are associated with milder disease than mutations occurring in exons 1-14 (34).

In contrast to this trend, other authors have described pedigrees with mutations in exons 1-14 of *RPGR*, such as in patient 3, that are also correlated with phenotypic high myopia in female carriers (8, 35, 36). Particularly, Banin et al. reported a missense substitution (c.g823a, p.Gly275Ser) within exon 8 in an Israeli family, where obligate carriers suffered from high myopia, low visual acuity, restricted visual fields, and reduced ERG amplitudes (36). However, this identical variant was also identified in two Danish families, where

obligate carriers had no visual complaints and normal to slightly diminished retinal function (37). Because the disease-related RPGR haplotypes in the aforementioned families were different, Banin suggested that additional genes linked to *RPGR* may explain the high phenotypic variability resulting from *RPGR* mutations and be related to the myopia observed in affected carriers (36). Exons 1-10 of *RPGR* encode a domain homologous to the Regulator of Chromosome Condensation 1 (RCC1), a guanine nucleotide exchange factor for Ran, consisting of seven blade-shaped beta sheets forming a beta-propeller structure (Figure 6) (12). Binding sites for proteins such as RPGR interacting protein 1 (RPGRIP1) and the delta subunit of rod cyclic GMP phosphodiesterase (PDE6δ) exist in the RCC1-like domain. The deletion (c.1100delC, p.Pro367Leufs*14) in patient 3 occurred in exon 10 of RPGR, indicating a potential role of N-terminal protein interactions in the pathogenesis of disease. Inositol polyphosphate-5-phosphatase 5E (INPP5E), a potential ciliary cargo protein that interacts with the N-terminus of RPGR, has been recently implicated in the pathogenesis of RPGR-associated ciliopathies and non-syndromic inherited retinal degenerations (38, 39).

While mutations in different regions of the *RPGR* gene can account for the phenotypic diversity observed in our cohort, it is more difficult to explain variability among patients who carry the same mutation. For example, in a case report of dizygotic twins, Walia et al. demonstrated that identical mutations in exon ORF15 manifested as clinically distinct cone-rod dystrophy in one twin and XLRP in his twin brother (40). Furthermore, descriptions of intra-familial variance in visual acuity, ERG response, and fundus features among female carriers of large pedigrees suggest that other factors such as genetic modifiers and X-chromosome inactivation (XCI) may influence disease severity (29, 41, 42). Nishiguchi et al. identified the (c.2405_2406delAG, p.Glu802Glyfs*32) variant, common to patient 4, in a Japanese male with a heterozygous frameshift variant (p.L206fs) in the NIMA Related Kinase 2 (*NEK2*) gene (43). Nishiguchi observed that zebrafish embryos with suppressed expression of *RPGR* and *NEK2* by *RPGR* and *NEK2* morpholinos were more likely to develop ocular abnormalities and photoreceptor dysfunction compared to zebrafish embryos suppressed by *RPGR* or *NEK2* morpholinos alone, hypothesizing that the *RPGR* allele may interact in trans with the *NEK2* locus to induce a deleterious effect beyond what could be accounted for by the loss of RPGR function itself (43). It is important to note that patient 4 presented with unilateral high myopia, which may be related to her history of refractive surgery, however this variant has been previously associated with a myopic phenotype in a female XLRP carrier of previous study (44). Similar to other X-linked diseases, the variable phenotype in carriers can be explained by random XCI. XCI ratio (mutant *RPGR* to wild type *RPGR*) has been shown to be negatively correlated with spherical equivalent, suggesting that eyes with a higher proportion of cells expressing mutant *RPGR* are more likely to be myopic (45). However, this contrasts with previous findings that exclude XCI skewing as a cause for differences in disease severity among carrier females (36). Recently, alterations in the $RPGR^{Ex1\text{-}19}$/$RPGR^{ORF15}$ ratio have been associated with ciliary length defects in fibroblasts isolated from male $RPGR^{ORF15}$ patients, further highlighting the complexity of *RPGR* gene defects (46).

Despite these differences, there are some common observations among our female patients. With no exception, all four carriers demonstrated signs characteristic of high myopia

including a tilted optic disc and posterior staphyloma (47). In three patients for whom fundus imaging was available, variable degrees of peripapillary atrophy were observed. Visual field tests were available for Patient 1 and 2, and showed constriction of the visual field. Additionally, all of our patients had a family history of at least one affected male in a previous generation.

In conclusion, this case series is the first to describe the clinical phenotype of the disease-causing *RPGR* variants harbored in Patients 1, 2, and 3 in female carriers. *RPGR* mutations lead to a phenotypic spectrum in female carriers, and previous studies have described high myopia as a common sign of RP in patients with *RPGR* mutations, particularly among carrier females (29). Although the exact mechanism of *RPGR*-related high myopia is still unclear, continued molecular diagnosis and description of phenotypes remain a crucial step in understanding the impact of *RPGR* mutations on visual function in female XLRP carriers. Our findings broaden the phenotypic spectrum of disease in female XLRP carriers with pathogenic *RPGR* mutations, which may facilitate appropriate genetic counseling and selection of candidates for future clinical trials.

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Disclosure of interest

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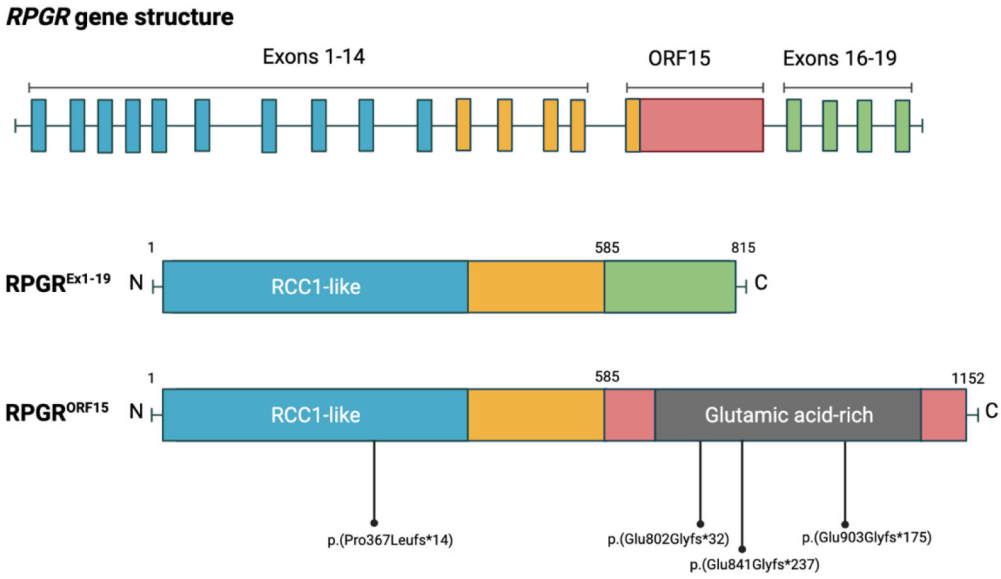

Figure 1.

RPGR gene and main protein isoforms. Schematic representation of the *RPGR* gene and constitutively expressed $RPGR^{Ex1\text{-}19}$ and retina-specific $RPGR^{ORF15}$ protein isoforms. Exons and the protein domains they encode are symbolized by the same color. The N-terminal domain (blue) shows homology to the Regulator of Chromatin Condensation (RCC1) protein and is common to both major RPGR isoforms. The location of ORF15 (red) and the Glutamic acid-glycine rich domain (gray) within $RPGR^{ORF15}$ are highlighted along with the approximate locations of mutations identified in this study.

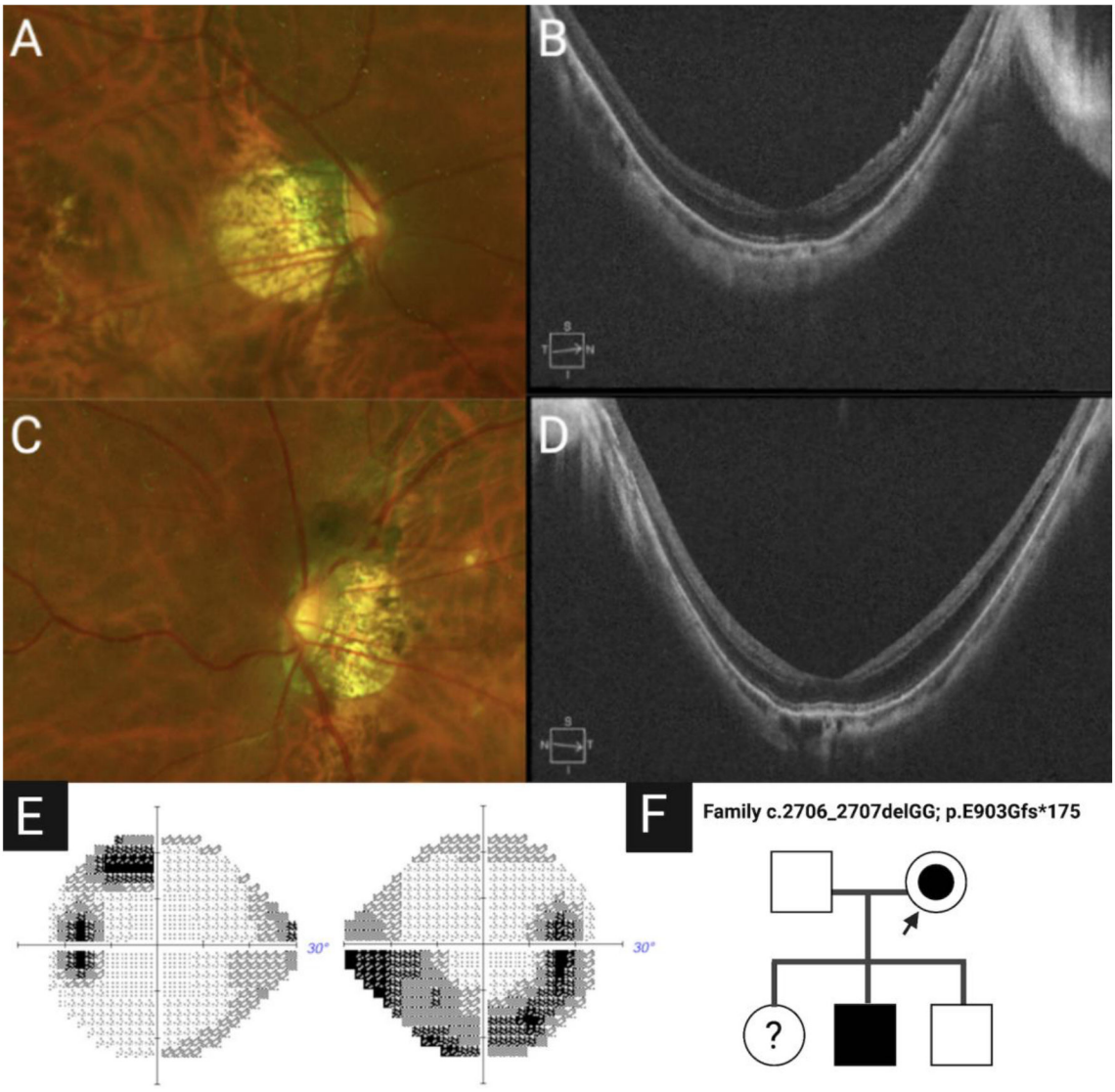

Figure 2.

Color fundus imaging, spectral-domain optical coherence tomography (SD-OCT), Humphrey Visual Field (HVF) testing, and family pedigree of Patient 1 (c.2706_2707delGG, p.Glu903Glyfs*175). Severely tilted optic nerves with large peripapillary atrophy and attenuated vessels in both eyes can be seen in images A and C. Posterior staphyloma of both eyes with retinal thinning are visible on SD-OCT in images B and D. 24-2 HVF shows a superior arcuate defect and nasal steps in the left eye (mean deviation of −9.07dB) and a dense inferior arcuate defect and early superior nasal step in the right eye (mean deviation of −13.76dB) in image E. (F) Pedigree of Family 1. Black squares (males) represent individuals diagnosed with RP. Dotted circles (females) represent carriers diagnosed with RP. The black arrow identifies the female proband and question marks represent individuals with unknown carrier status.

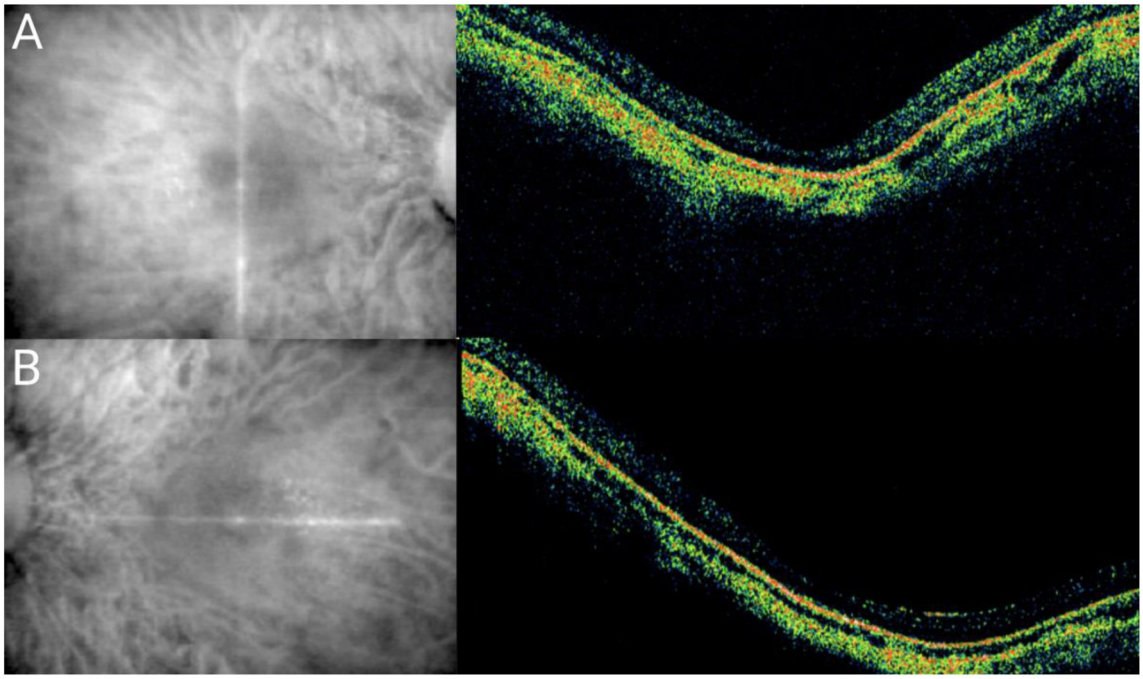

Figure 3.
SD-OCT examination of Patient 2 (c.2517_2518delAG, p.Glu841Glyfs*237). There is retinal thinning of the macula and posterior staphyloma in both eyes.

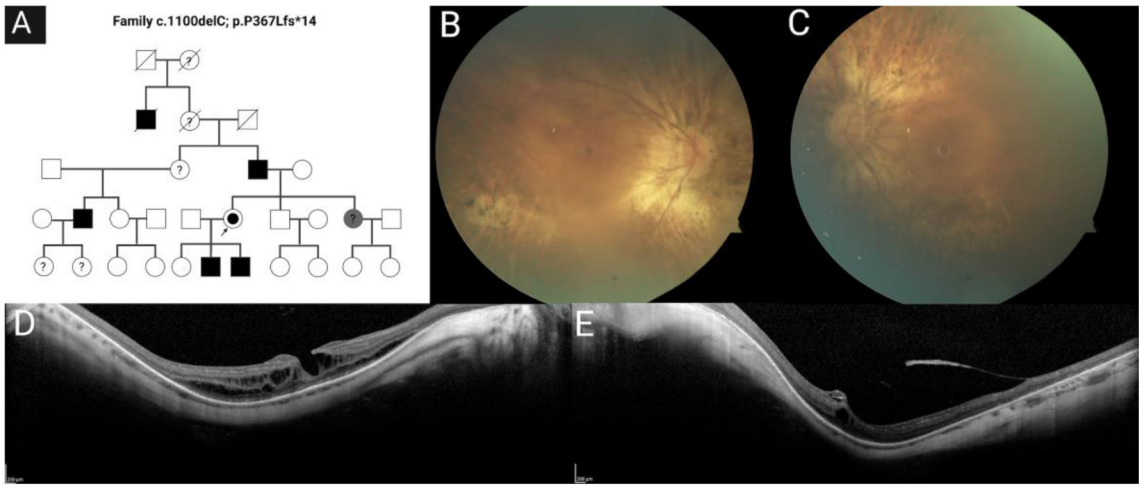

Figure 4.

Family pedigree, color fundus imaging, and spectral-domain optical coherence tomography (SD-OCT) of Patient 3 (c.1100delC, p.Pro367Leufs*14). (A) Pedigree of Family 3. Black squares (males) represent individuals diagnosed with RP. Dotted circles (females) represent carriers diagnosed with RP. Family members diagnosed with high myopia are represented in gray. The black arrow identifies the female proband. Black lines designate deceased individuals and question marks represent individuals with unknown carrier status. Tilted optic nerves with peripapillary atrophy and attenuated vessels can be seen in images B and C. SD-OCTs show posterior staphyloma of both eyes with retinal thinning in images D and E. A lamellar hole, vitreomacular traction and intraretinal cysts can be appreciated in image D.

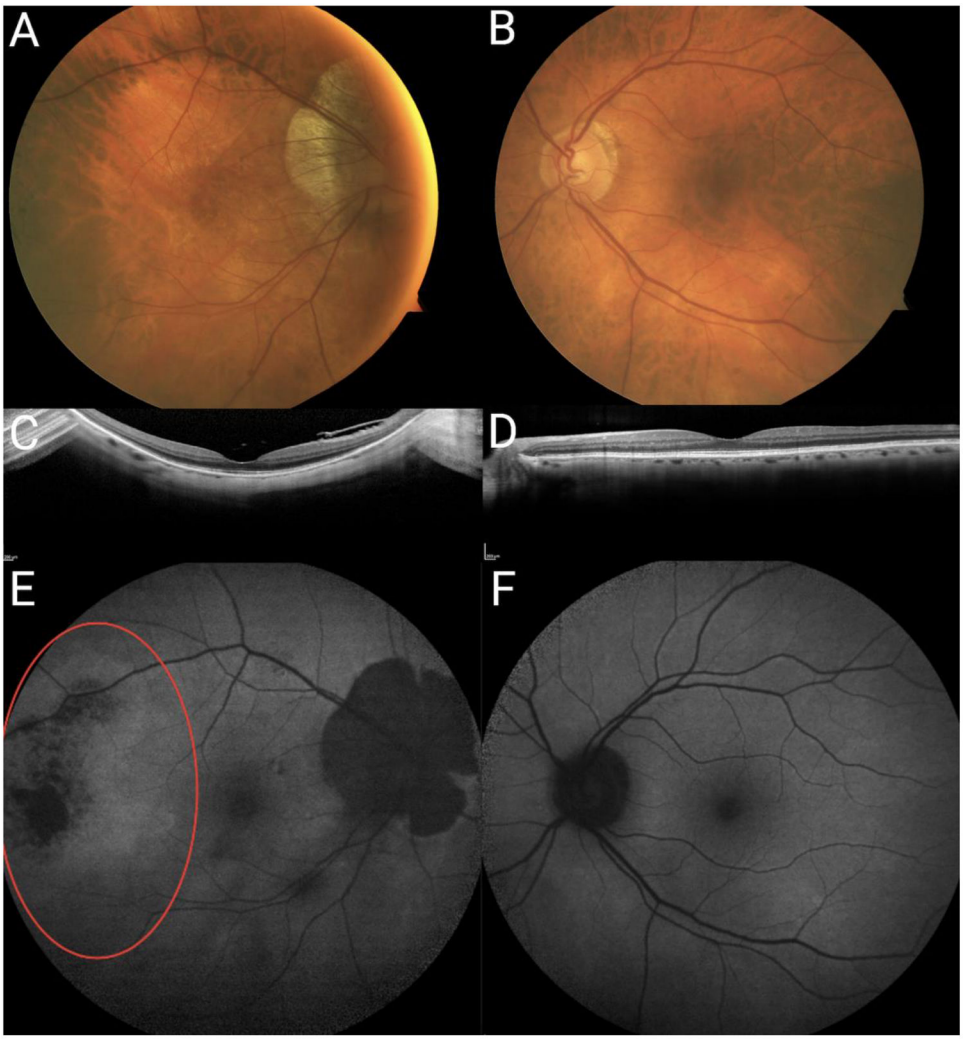

Figure 5.

Color fundus imaging, spectral-domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF) imaging of Patient 4 (c.2405_2406delAG, p.Glu802Glyfs*32). Image A shows a tilted optic nerve with a large area of peripapillary atrophy in the right eye. Mild peripapillary atrophy can be appreciated in the left eye in image B. There is posterior staphyloma visible on SD-OCT in image C. FAF imaging shows a hyperfluorescent lesion surrounded by a hypofluorescent area in the periphery of the right eye (red circle) in image E.

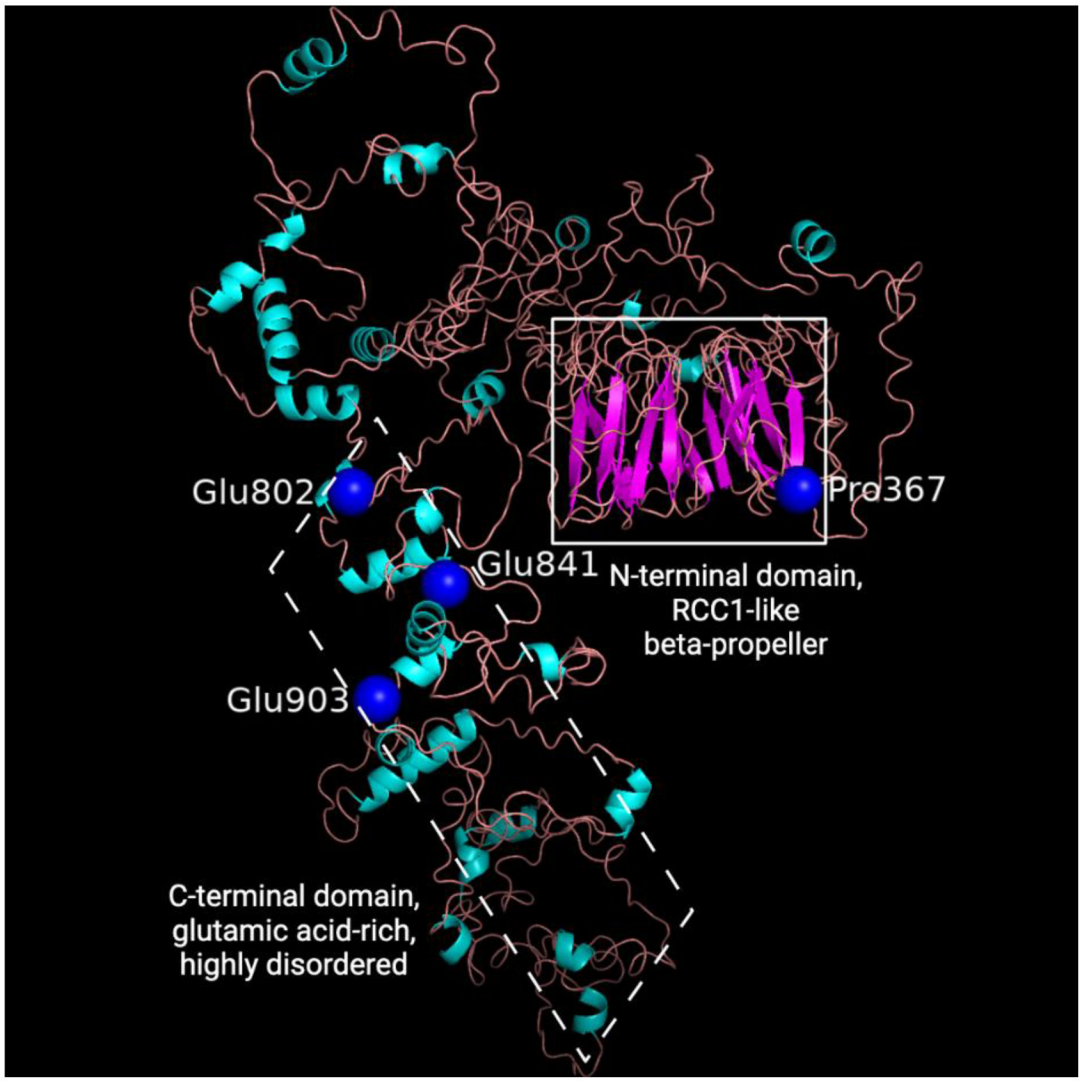

Figure 6.

RPGR Protein Model. The N-terminal RCC1-like domain (solid white box) is formed by seven blade-shaped beta sheets forming a beta-propeller structure. The C-terminal domain (dashed white box) is highly disordered and rich of glutamic acid residues. Location of frameshift variants identified in the present study are shown as blue spheres.

Table 1.

Patient characteristics.

Case	Age/Gender	Mutation	BCVA	Refraction, RE/LE (Diopters)	Fundus exam
1	50/F	c.2706_2707delGG p.(Glu903Glyfs*175)	OD: 20/50 OS: 20/20	OD: −13.00 OS: −11.50	Posterior vitreous detachment, peripapillary atrophy, tilted optic nerves, posterior staphyloma, macular coloboma
2	30/F	c.2517_2518delAG p.(Glu841Glyfs*237)	OD: 20/100 OS: 20/70	NA	Vascular attenuation, pigmentary changes, tilted optic nerves, posterior staphyloma
3	56/F	c.1100delC p.(Pro367Leufs*14)	OD: 20/60 OS: 20/80	OD: −16.00 OS: −15.25	Pigmentary changes, nuclear sclerotic cataracts, vascular attenuation, tilted optic nerves, peripapillary atrophy, posterior staphyloma, vitreomacular traction
4	80/F	c.2405_2406delAG p(Glu802Glyfs*32)	OD: 20/40 OS: 20/25	OD: −7.00 OS: −0.75	Tapetal-like reflex, peripapillary atrophy, posterior staphyloma, vitreomacular traction

Abbreviations: BCVA, best corrected visual acuity; OD, right eye; OS, left eye; NA, not available.