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Identification of Novel Nonsense *RPGR* Variant Causing Mild X-Linked Cone-Rod Dystrophy and Myopia

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Abstract

Background: Mutations in the *RPGR* gene are associated with rod-cone or cone-rod dystrophy, the latter associated with mutations at the distal end. Cone-rod dystrophy (CRD) is a subgroup of hereditary retinal disorders characterized by the primary degeneration of cone photoreceptors often followed by progressive loss of rod photoreceptors in the peripheral visual field. Purpose: The aim of this study was to describe the milder CRD phenotype associated with a novel pathogenic variant c.1905 + 223C > T (p.Q710X) found in *RPGR* which results in shortening of the photoreceptor specific isoform *RPGR* ^{ORF15}. Method: An 11-year-old boy with symptoms of CRD and two female relatives were referred for detailed ophthalmic examinations. Genetic testing was performed by next-generation sequencing of clinical exome followed by Sanger sequencing for segregation analysis. Results: Genetic analysis identified a novel variant in ORF15 of the *RPGR* gene (c.1905 + 223C > T, p.Q710X) in the proband considered as pathogenic according to the American College of Medical Genetics and Genomics (ACMG) standards. Segregation study identified the mutation in a heterozygous state in the mother and her sister. Detailed ophthalmological examination revealed slightly reduced color vision and scattered grayish point-like deposits in the posterior pole of the fundus in the male patient. All mutation carriers were myopic. Conclusion: We report a novel pathogenic *RPGR* variant in a Bulgarian patient with clinical features compatible with the CRD diagnosis. This condition is inhe-

rited as an X-linked dominant trait in its familial form presenting with a mild CRD phenotype in the male hemizygous proband and a moderate to high myopia in the female heterozygous carriers.

Keywords

Cone-Rod Dystrophy, Myopia, *RPGR*, Novel Mutation

1. Introduction

Cone-rod dystrophy (CRD) is an inherited retinal disorder (IRD) with prevalence 1 in 40,000, characterized by visual loss, color vision defects, decreased sensitivity in the central visual field, and a variable degree of nystagmus and photophobia. It represents an important cause of visual impairment in children and adults. CRD is characterized by progressive loss of cone photoreceptor function followed by progressive loss of rod photoreceptor function and is often accompanied by retinal degeneration [1]. Over time, affected individuals develop night blindness and loss of peripheral field. At end stage, CRD may not differ from the rod-cone dystrophies, also called retinitis pigmentosa (RP, with prevalence of 1 in 4000) [2]. Typically, fundus imaging of CRD patients presents pigmentary deposits resembling bone spicules (often in macular or paramacular area), retinal vessels attenuation, pale optic disc and various degrees of retinal atrophy [2]. Progressive degenerative changes of the macula occur rarely. X-linked cone-rod dystrophy (XLCRD) is a rare progressive retinal degeneration and usually manifests with early visual impairment affecting predominantly male patients (hemizygotes), who are legally blind before the end of their third decade, while carrier heterozygous women present various degrees of visual dysfunction, ranging from asymptomatic to severe phenotype [3]. The retinas of some affected males had a bronze-green tapetal-like sheen. The degree of rod-photoreceptor involvement can be variable, with degeneration increasing as the disease progresses. Although penetrance appears to be nearly 100%, there is variable expressivity with respect to age at onset, severity of symptoms, and findings [4]. Moderate or high myopia is often secondary to XLCRD phenotype both on patients and carrier [5].

RPGR gene is a major cause of X-linked retinitis pigmentosa (XLRP) which is the most severe type of RP (OMIM #300029), and is also responsible for XLCRD (OMIM #304020) and atrophic macular degeneration (OMIM #300834) [6]. The *RPGR* gene encodes the retinitis pigmentosa GTPase regulator (RPGR) protein and is able to express multiple retinal isoforms through alternative splicing. The two major isoforms include $RPGR^{1\text{-}19}$, which spans exons 1 - 19 and encodes an 815-aa polypeptide, and $RPGR^{ORF15}$, which spans exons 1 - 15 plus a part of intron 15 and encodes a 1152-aa polypeptide [7] [8]. It shares exons 1 - 14 with $RPGR^{1\text{-}19}$ plus the exon ORF15, encoding 567 amino acids with a repetitive glycine and glutamic acid-rich domain and a conserved basic C-terminal domain.

In addition to these two major transcripts of the gene, *RPGR* encodes complex alternative spliced transcripts and many novel tissue-specific exons have been reported. All of the transcripts encode an amino (N)-terminal RCC1-like domain that is structurally similar to the RCC1 protein, a guanine nucleotide exchange factor for the small GTP-binding protein, Ran [9]. *RPGR* $^{1\text{-}19}$ is widely distributed in ciliated tissues, whereas *RPGR* ^{ORF15} is found primarily in the connecting cilia of photoreceptor cells, predominantly in the outer segment of rod photoreceptors [10]. Due to the presence of highly repetitive purine-rich sequences, the exon ORF15 is a mutational hotspot for XlRP (accounting for 2/3 of all disease-causing mutations) and for most XLCRD cases [11].

Most reported mutations in the first 14 exons are nonsense or frameshift mutations that can lead to nonsense-mediated decay of the mRNA (NMD), and low or absent levels of the transcript. In contrast, nonsense or frameshift mutations in ORF15 are less likely to lead to NMD since this is the last exon of the transcript [12], and a series of truncated proteins of varying length can be found [13].

From a genetic point of view, IRDs displays locus and allelic heterogeneity, with more than 300 causative genes (https://sph.uth.edu/retnet/) that make the genetic characterization very difficult. The advent of next-generation sequencing (NGS) has opened new frontiers in genetic diagnostics of IRDs, exploiting the high-throughput parallel sequencing and the simultaneous analysis of many samples. The overall mutation detection rate for IRDs is variable and ranges from 36% to 60%, leaving many cases still genetically unsolved [14]. Although whole-exome sequencing (WES) is a more appropriate tool for genetic diagnostics of the extreme heterogeneous IRDs than gene panels, commercialized gene panels comprising all known disease-related genes, called "clinical exome" have been successfully applied for genetic testing of retinopathies [14] giving a diagnostic yield of over 80% for IRD cases in Bulgaria (personal unpublished data).

Here, we describe a male patient with clinical suspicion of CRD in whom clinical exome sequencing (CES) found a novel nonsense mutation in the exon ORF15 (c.1905 + 223C > T, p.Q710X) of *RPGR* gene. The presence of *RPGR*-c.1905 + 223C > T variant in the myopic female carriers is consistent with X-linked dominant mode of inheritance and milder phenotype in the studied pedigree.

2. Material and Methods

Patient and clinical assessment

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Medical University of Sofia (Bulgaria). Written informed consent form was obtained from all participants.

An 11-year-old boy complaining from impaired vision, photophobia, and myopia noticed since about 7 years of age, was referred by the University Hospital "Alexandrovska", Sofia. The proband underwent a complete ophthalmic exami-

nation, including autorefractometry after cycloplegia (Canon autorefractometer RK-F2), determination of best-corrected visual acuity (BCVA), intraocular pressure (IOP), slit lamp examination of the anterior eye segment, automated perimetry (Octopus perimeter), slit lamp examination of the ocular fundus using + 90D lens with dilated pupils, multifocal electroretinogram (mfERG, RETIscan Standard 6.11), fundus photograph (Eidon true color confocal scanner), Ishihara color vision test, fundus autofluorescence (FAF, Eidon true color confocal scanner), optical coherence tomography (OCT, NIDEK, RS 3000).

In order to study the genetic basis of the phenotype segregating in this pedigree, we collected peripheral blood samples from the proband for CES analysis as well as from asymptomatic and myopic family members available for segregation study.

Genetic analysis

Peripheral blood samples of the proband, his parents and the sister of his mother (Figure 1) were collected for a molecular genetic analysis and DNA was extracted from leukocytes using Chemagic DNA blood 10 k kit H1 and Chemagen Magnetic Separation Module (PerkinElmer®, Waltham, MA, USA) according the manufacturer's protocol. Targeted NGS was performed using TruSight One sequencing panel (Illumina, San Diego, CA, USA), which includes 4813 genes associated with known OMIM diseases. TruSight one sequencing

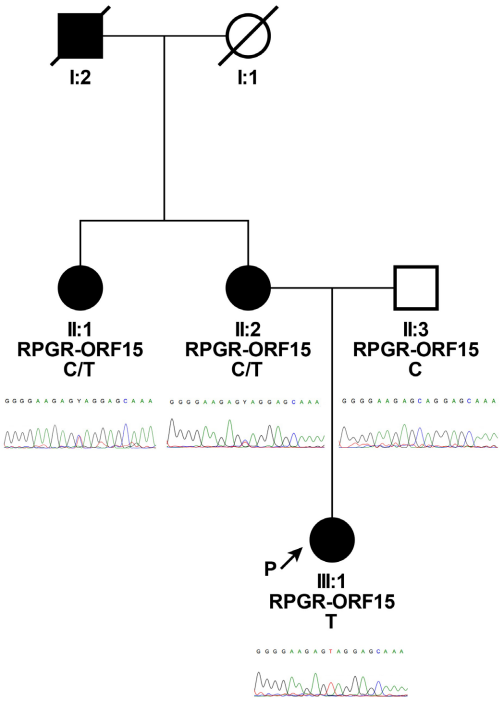


Figure 1. Pedigrees of CRD family and segregation analysis of identified c.1905 + 223C > T in *RPGR* ^{ORF15}. Individuals are identified by pedigree number. Squares indicate males, circles indicate females, slashed symbols indicate deceased, solid symbols indicate affected individuals, open symbols indicate unaffected individuals, black arrow indicates the proband. Sequencing chromatograms showing mutation segregation in each pedigree is presented.

panel includes all reagents required for amplification, amplicon enrichment, and indexing of samples, and protocol was followed according to the manufacturer's instructions. After preparation of the sequence libraries, MiSeq next-generation platform (Illumina) was used to sequence 150-bp paired-end reads.

Assessment of the pathogenicity of candidate variants

Filtered variants with coverage < 20× and those with MAF higher than 0.005 (in case of presumed autosomal recessive mode of inheritance) in at least one of the searchable databases (dbSNP or gnomAD) were excluded. To detect known disease-associated mutations, the remaining variants were compared to human mutation databases such as HGMD and ClinVar. The pathogenicity of novel SNVs was predicted by PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), SIFT (http://sift.bii.a-star.edu.sg), MutationAssessor (http://mutationassessor.org/r3/), and FATHMM (http://fathmm.biocompute.org.uk/) softwares. Pathogenicity of variants was ascertained according to the criteria of American College of Medical Genetics (ACMG) [15], which classify variants according to 5 categories (benign, likely benign, uncertain significance, likely pathogenic, and pathogenic).

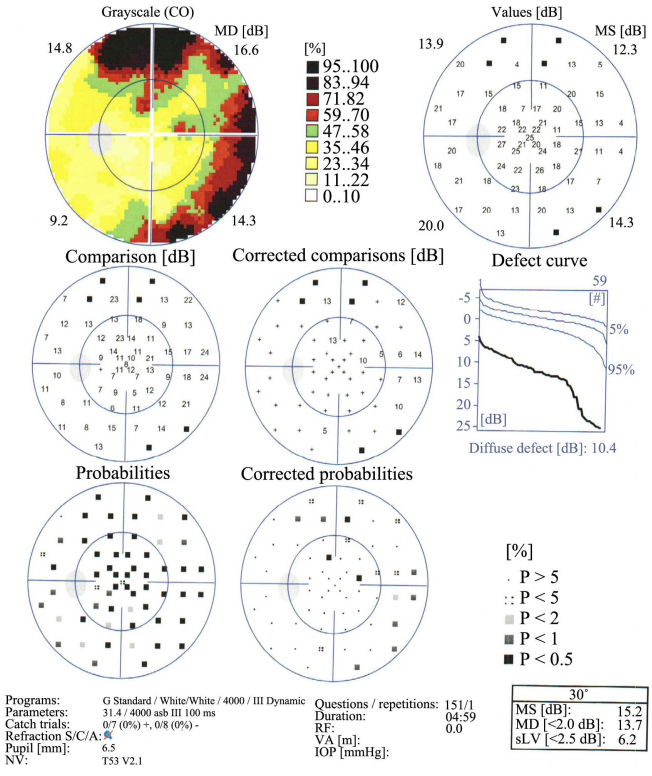
The Identified variant was confirmed by Sanger sequencing on an ABI 3130XL Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). The DNA fragments containing the variants were amplified by PCR with specific primers and were sequenced using the Big Dye 3.1 Terminator Sequencing Kit. Sanger sequencing was also employed for segregation study.

3. Results

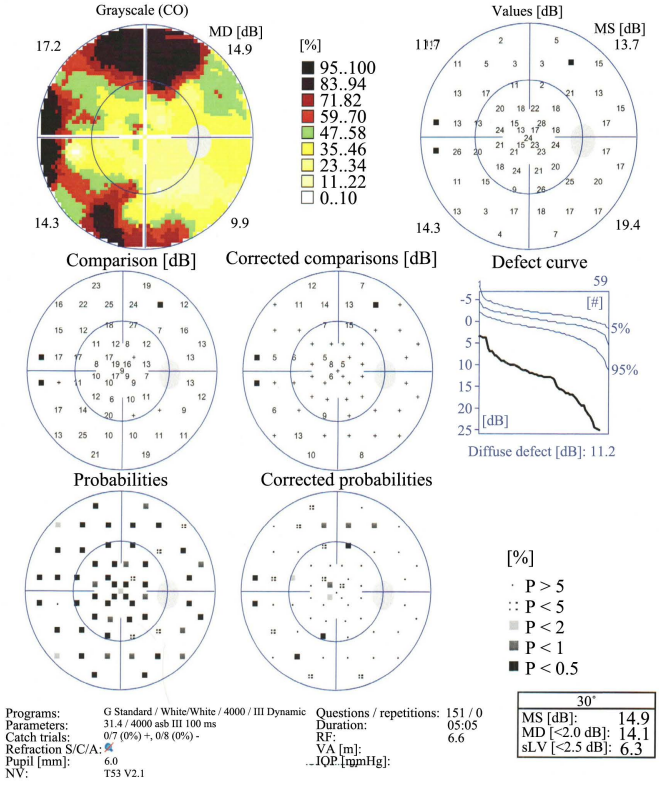
Clinical data

Patient has suffered from symptoms consisting with a mild form of CRD, including decreased sensitivity in the central and peripheral visual field, slightly reduced visual acuity, and myopia with no nyctalopia and color vision defects observed. BCVA was declined to 0.7 (metric) in both eyes (with spherical correction of −1.0 D in the left eye). Automated perimetry showed a bilateral peripheral and central perimetric defect (**Figure 2(a)** and **Figure 2(b)**). Ophthalmic examination revealed grayish point-like deposits scattered within the posterior pole of the fundus, mainly in the paramacular area, but no attenuation of the retinal vessels, optic disc pallor and retinal atrophy were observed (**Figure 3(a)** and **Figure 3(b)**). Fundus autofluorescence did not reveal a pathologic finding (**Figure 4(a)** and **Figure 4(b)**). The optical coherence tomography showed normal retinal thickness and absence of any pathological changes (**Figure 5(a)** and **Figure 5(b)**). The Ishihara test revealed no abnormalities in color perception. ERG profile of the proband demonstrated normal morphology and polarity with a reduced amplitude of scotopic and photopic response (20% for the right eye and 25% for the left eye) and prolonged latency (**Figure 6**).

Patient's mother (II: 2, 44 y) and her sister (II: 1, 50 y) presented with moderate (−4.0 diopters) and high myopia (−8.0 diopters), respectively, from their

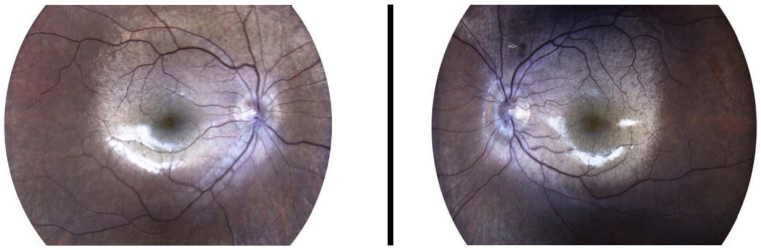


(a)



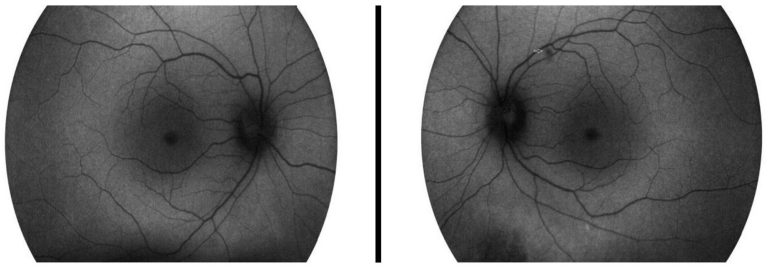
(b)

Figure 2. A bilateral peripheral and central perimetric defect in the 11-year-old proband ((a)—right eye, (b)—left eye).



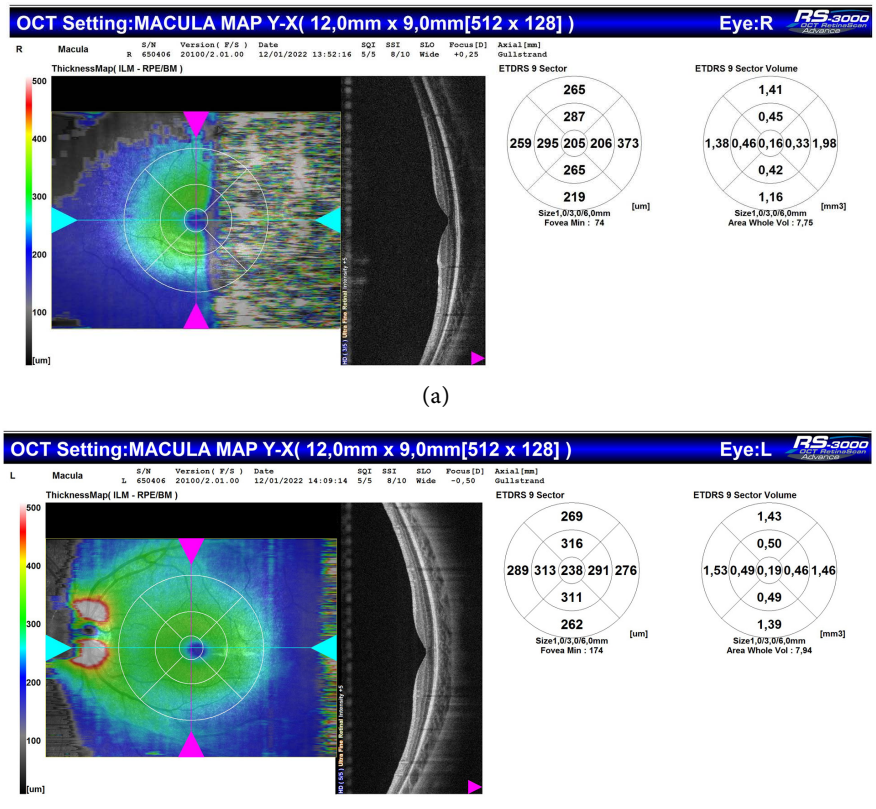
(a) (b)

Figure 3. Fundus photograph (Eidon true color confocal scanner) in the 11-year-old proband ((a)—right eye, (b)—left eye, white arrow—artifact from vitreous opacity).



(a) (b)

Figure 4. Fundus autofluorescence in the 11-year-old proband ((a)—right eye, (b)—left eye, white arrow—artifact from vitreous opacity).



(a)

(b)

Figure 5. Optical coherence tomography in the 11-year-old proband ((a)—right eye, (b)—left eye).

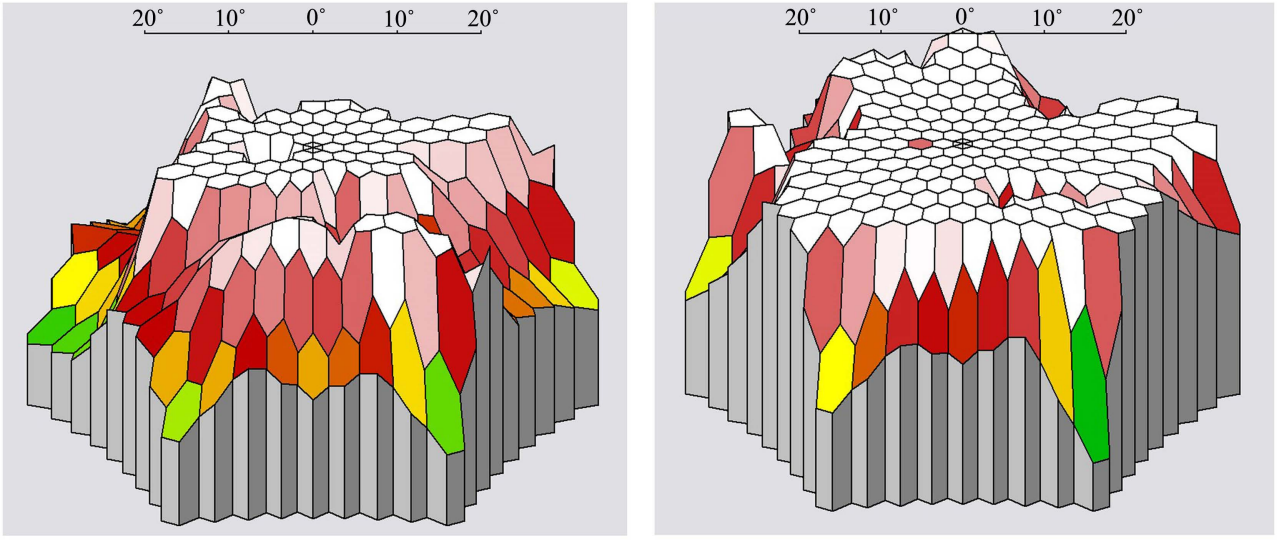


Figure 6. Multifocal ERG in the 11-year-old proband ((a)—right eye, (b)—left eye).

20s. Fundus and electrophysiological examination of the two sisters (II: 1 and II: 2) showed no abnormalities. The ophthalmic diagnostic data are documented in Table 1. There was no older male carrier available for study the progression during follow-up years.

Genetic findings

Family pedigree is shown on Figure 1. Genetic testing of proband's DNA identified a novel variant c.1905 + 223C > T (p.Q710X) in the *RPGR* ^{ORF15}. The mean sequence coverage was over 100× and more than 95% of target bases were covered with at least 20×. A novel variation, c.1905 + 223C > T, in *RPGR* gene resulting in a stop codon and premature translational termination at position 710 (p.Q710X) of the normal 1152-aa polypeptide was identified as the potential disease-causing nonsense mutation. The novel *RPGR* variant has not been reported in the context of clinical significance (ClinVar, HGMD) and is not found in the gnomAD population database and dbSNP. According to the ACMG classification, c.1905 + 223C > T (NM_001034853.1) was classified as a pathogenic because of 1) its type of null variant (PVS1), 2) absence in healthy individuals (PM2), 3) co-segregation with the disease in the family (PP1), 4) occurrence in a gene that has a low rate of benign missense variation (PP2), 5) computational tools predict a deleterious effect on the coded gene product (PP3) and 6) phenotype and family history specific for X-linked disease with a monogenic etiology (PP4).

Genomic DNA of collected family members was further analyzed by Sanger sequencing. Novel *RPGR* variant c.1905 + 223C > T was confirmed for the proband as a hemizygous mutation and for the myopic female members (mother and aunt) who were heterozygous carriers (Figure 1). The change was not found in the unaffected father. Therefore, the novel *RPGR* change c.1905 + 223C > T was shared by affected patients.

Table 1. Clinical characteristics of patients included in the study.

Subject No.	Age at the First/Last Examination (years)	Age at Onset	BCVA (Decimal)		Intraocular pressure (mmHg)		Ishihara		Refraction (Diopter)		Visual Field		Fundus features	Fundus autoFluorescence	OCT		mfERG	
			BE		RE	LE	BE		RE	LE	BE		BE	BE	BE		RE	LE
III: 1	7/11	Childhood: Photophobia, refraction error (myopia), reduced visual acuity, impaired central vision	0.7		11.3	10.5	Normal		Normal	−1.0	Paracentral scotoma		Scattered grayish point-like deposits in the posterior pole mainly in the paramacular area, normal optic discs and retinal vessels	Normal	Normal retinal thickness and absence of pathological changes		Reduced amplitude of 20%	Reduced amplitude of 25%
II: 1	20/50	Childhood: No complains. Early 20s: Refraction error (myopia)	1.0		Not tested	Not tested	Normal		−8.0	−8.0	Normal		Normal	Not tested	Not tested		Not tested	Not tested
II: 2	20/44	Childhood: No complains. Early 20s: Refraction error (myopia)	1.0		Not tested	Not tested	Normal		−4.0	−4.0	Normal		Normal	Not tested	Not tested		Not tested	Not tested

Abbreviation explanation: LE - Left Eye, RE - Right Eye, BE - Both Eyes, BCVA - Best Corrected Visual Acuity, OCT - Optical Coherence Tomography, mfERG - multifocal Electroretinography.

4. Discussion

XLCRD is a rare, progressive inherited retinal degeneration which primarily affects the cone photoreceptors. In affected men the disease is characterized by early onset (childhood) and rapid progression of vision loss, resulting in legal blindness by the end of 30s. In contrast to men, most affected women show extremely variable symptoms, ranging from asymptomatic electrophysiological abnormalities to severe retinal disease [16], and legal blindness occurs at approximately 30 - 40 years of age [17]. Inactivation of the X chromosome is believed to contribute to more severe phenotype [18], however, presence of other modifying genetic factors has also been discussed [19]. According to literature, *RPGR* carriers are most likely to present symptoms that might be grouped in four main patterns of fundus appearance: normal or near normal pattern, a tapetal reflex, focal or patchy pigmentary retinopathy limited to a quadrant or hemisphere, and three or more quadrants of bone spicule pigmentation or atrophy [20]. Most patients complain of myopia, with 50% - 72% having a refractive error of greater than −6 diopters [21].

RPGR is a major locus for XLCRD. Mutations that cause CRD are predominantly located at the 3' end of the ORF15 exon in *RPGR* [22]. *RPGR* is expressed in retinal photoreceptors where it is located in the connecting cilia of both rods and cones [23] and being a regulator of protein trafficking, RPGR is involved in maintaining the structure and function of mature cilia. Defects in *RPGR* result in a severe retinal ciliopathy, which finally leads to retinal degeneration [24].

In this study, we report a Bulgarian family affected by XLCRD. Detailed clinical diagnostic data describing the phenotype of the proband are presented. Genetic analysis identified a novel hemizygote nonsense variant (c.1905 + 223C > T, p.Q710X) in *RPGR* gene that co-segregates with the heterozygote female carriers as high myopia. Thus, the variant p.Q710X in *RPGR* represents a novel disease-causing mutation leading to mild X-linked CRD in male and moderate to high myopia in female patients.

The nonsense mutation (c.1905 + 223C > T, p.Q710X) identified in this study is located in exon ORF15, considered the major disease-associated locus due to its highly repetitive purine-rich sequence [25]. The c.1905 + 223C > T mutation is localized before the repetitive glycine and glutamic acid-rich domain (AD) and similar to other previously described variant would result in shortening of RPGR polypeptide by removing the Glu-Gly rich domain and the conserved basic C-terminal domain (BD) [22]. The nonsense mutation that authors have reported creates a truncated protein and the shortened protein did not contain the Glu-Gly rich domain. The N-terminal RCC1-like domain, which plays a role in *RPGR* localization to cilia by binding to *RPGRIP1* and *RPGRIP1L* [26], and also mediates complexation of *RPGR* with SMC1/3, PDEδ, and Rab8, which are critical to cilia functions [9], is preserved in the truncated mutant.

Previous report from Wang *et al.* demonstrated that the hemizygous males who carried a newly found mutation c.2383G > T (p.E795X) in exon ORF15 suffered from typical for CRD symptoms such as early nyctalopia, progressive visu-

al impairment, color vision defects and decreased sensitivity in the central visual field, followed by progressive loss in peripheral vision. Female carriers showed normal phenotype [22]. In contrast to this report, the patient described here presents a mild phenotype including decreased sensitivity in the central and peripheral visual field, slightly reduced visual acuity, and myopia with no nyctalopia and color vision defects observed. There was no history of retinal disease in female carriers except for myopia seen in the mother and her sister. Nevertheless, the female carriers were not examined thoroughly at our institution therefore a mild retinal phenotype cannot be excluded.

It has been previously shown that a novel C-terminal extension variant c.3457T > A (X1153Lext * 38) due to the loss of the terminal *RPGR* ^{ORF15} codon is associated with myopia and adult-onset cone dystrophy in three patients. Considering that the mutation in the last codon resulted in cone-dystrophy in the three patients the authors hypothesize that the involvement of rods diminishes downstream of the ORF15 exon. In addition, it is possible that the cone involvement increases simultaneously with the decrease of rod involvement or else is present at the same level in all phenotypes and becomes more prominent with diminished rod involvement [20]. This is comparable to our observation, as our patient had myopia and typically early central vision decrease. Minimal progression during the follow-up 4 years suggests a relatively stable disease after the initial impairment of the central vision.

Given the complexity of *RPGR* function and network, the pathogenic mechanism resulting from *RPGR* mutations remains to be clarified. It remains unclear until now why some mutations in *RPGR* cause RP and others cause CRD. Literature on why some ORF15 mutations affect rods, and others cause predominantly cone degeneration is published [27]. It seems attractive to speculate that mutations in the exon ORF15 are more often found in CRD cases, whereas mutations in the exon 1 - 14 are more often found in RP [22] [28].

5. Conclusion

In summary, our findings have identified a novel point mutation in the terminal codon of *RPGR* ^{ORF15}, c.1905 + 223C > T, p.Q710X, that contributes to a milder phenotype consistent with X-linked CRD (in hemizygotes) and moderate to high myopia (in heterozygotes) and further broadens the spectrum of *RPGR* mutations.

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Disclosure Statement

The authors report no conflict of interest.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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