Title: *RPGR*-associated Retinopathy – Clinical Features, Molecular Genetics, Animal Models and Therapeutic Options

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Abstract

Retinitis Pigmentosa GTPase Regulator *(RPGR)* gene sequence variants account for the vast majority of X-linked Retinitis Pigmentosa (RP), which is one of the most severe forms of RP. Symptoms of nyctalopia typically begin in childhood, with increasing loss of peripheral visual field during teenage years, and progressive central visual loss during the second to fourth decade of life. There is however marked intra- and interfamilial phenotypic heterogeneity both in affected males and carrier females. There is now a far greater understanding of the range of phenotypes associated with variants in this gene; including rod-cone dystrophy, cone-rod dystrophy, cone dystrophy, macular dystrophy and non-ocular phenotypes. There are also increasingly established genotype-phenotype associations and structure-function correlations. *RPGR* is involved in ciliary function, with ciliary dysfunction now recognized as the mechanism underlying a large proportion of inherited retinal disease. There has been significant progress in both identifying naturally occurring animal models and developing novel models to define the underlying disease mechanisms and to test gene replacement therapy, in addition to advances in human retinal imaging, culminating in completed and planned clinical trials. These significant developments will be discussed.

Introduction

Hereditary retinal disorders are now the leading cause of blindness in working age adults in England and Wales, and the second commonest in childhood [1]. Retinitis pigmentosa (RP), a group of genetically and phenotypically diverse disorders, affects ~ 1:3000 to 1:4000 and is inherited as an autosomal dominant, recessive or X-linked (XL) trait; which are estimated to account for 30-40%, 45-60% and 5-15% of cases respectively [2-6]. X-linked retinitis pigmentosa (XLRP) is particularly severe, with early-onset in childhood, progressing to severe visual impairment by the third to fourth decade. Retinitis Pigmentosa GTPase Regulator *(RPGR)* gene sequence variants account for 70-80% of XLRP [7-9]**,** *RP2* variants for a further 5-20% [8-12], and a third gene, *OFD1* has been identified as a rare cause of XLRP [13]. This review focuses on the molecular genetics and phenotypic features of *RPGR* retinopathy, animal models and therapeutic options.

Molecular Genetics of *RPGR*

RPGR was first identified as a cause of XLRP in 1996, composed of 19 exons and encoding a 90kDa protein product, with exons 2-11 coding for a structure similar to regulator of chromosome condensation 1 (RCC1) at the N-terminus [7 14]. RCC1 is a well-characterised protein that functions as a guanine nucleotide exchange factor for Ran (a Ras-related nuclear protein) and is thought to play an important role in nucleo-cytoplasmic transport and regulation of cell division [15 16]. Further analysis identified a transcript with a novel 3' terminal exon known as exon open reading frame 15 (ORF15) that includes exon 15 and a portion of intron 15 [17]. Only 10-20% of patients with XLRP harboured disease-causing sequence variants in *RPGR* prior to

the discovery of ORF15. The ORF15 exon has an unusual repetitive sequence encoding 567 amino acids rich in glycine and glutamic acid residues that is a "mutational hotspot", harbouring approximately 60% of all XLRP variants, thus underlying the majority of XLRP [17]. To date, over 300 variants have been identified in *RPGR* [18 19].

There are multiple *RPGR* isoforms arising from alternative splicing [20-24] or post-translational modification [25]. These isoforms are expressed in different amounts in different tissues (lung, kidney, retina, brain, testis); suggesting tissue-specific splicing with tissue-specific functions. The two major *RPGR* isoforms are the constitutive *RPGR* exon 1-19 and *RPGR* ORF15 [16], with *RPGR* ORF15 representing the isoform that is most highly expressed in retina [17]. To the best of our knowledge, all disease-causing variants are found in exons present in isoform *RPGR* ORF15, with only one in exons 15-19 [26], supporting the importance of the *RPGR* ORF15 isoform in the retina.

RPGR Interacting Proteins and Function

RPGR comprises an RCC1-like domain at its N-terminus, and the predicted function of the unusual C-terminal ORF15 protein sequence is not known. As illustrated in Figure 1, RPGR is localised predominantly to the photoreceptor connecting cilium [24], which is the equivalent of the transition zone of motile and primary cilia. An RPGR protein interaction network has been established, either through genetic studies identifying disease genes with overlapping symptoms, or through targeted functional studies, or a combination of both [16 27-29]. Some of the principal interacting proteins will be alluded to herein. Retinitis pigmentosa GTPase regulator-

interacting protein (RPGRIP1) localizes to the connecting cilia and is thought to hold RPGR in this locale [28]. Similarly, retinitis pigmentosa GTPase regulator-interacting protein-1 like protein (RPGRIPL1), delta subunit of rod cyclic GMP phosphodiesterase (PDEδ), structural maintenance of chromosomes 1 and 3 (SMC1/3), GTPase Rab8A, nephrocystin-5, and whirlin also have been shown to interact with RPGR [29-35].

Although the function of RPGR is not fully understood, information from biochemical studies and the phenotypes in patients and animal models, strongly suggests that it plays a role in the transport of phototransduction components and other outer segment proteins across the connecting cilium. Biochemical studies have shown that RPGR-ORF15 localises to the connecting cilium of the photoreceptor and binds to the basal body and the axoneme [30 36]. Involvement of RPGR-ORF15 in transport is suggested in immunoprecipitation experiments that show that RPGR interacts with γ-tubulin, subunits of Kinesin II and dynein microtubule motor protein complexes, and intraflagellar transport polypeptide 88 (IFT88) [30]. However, these interactions do not exclude that RPGR-ORF15 may be involved as cargo in these processes, rather than as an active component.

The most prominent and consistent evidence for a role in ciliary transport is provided by various post-mortem studies that have utilised immunohistochemical techniques to demonstrate opsin mislocalisation within the photoreceptor structure in human, canine and mice models of RPGR-deficient carriers and affected subjects [37-41]. Opsin molecules are G-protein coupled receptors integral to visual phototransduction. These are assembled within the organelles of the photoreceptor inner segment and systematically transported via the connecting cilium to their final

destination in the outer segment where they are contained within the disc membranes [42].

Cone and rod opsin mislocalisation to photoreceptor inner segments, perinuclear regions and synaptic terminals has been shown in human and canine subjects [37 40 41]. Cone but not rod opsin mislocalisation to similar regions have also been found in mice models, together with a reduction in rhodopsin levels within the outer segments [38 39].

The structure of the connecting cilium is not compromised in RPGR-deficient photoreceptors, and the presence of correctly localised opsins and relatively well preserved vision in the early stages of disease indicate that RPGR plays a facilitative rather than an essential role in the transport process [39]. A role in docking and selection of cargo at the basal body has been suggested [30 36].

How opsin mislocalisation affects photoreceptor viability to cause retinal degeneration remains unclear. A mechanism whereby ectopic G-protein activity is stimulated by mislocalised opsin molecules leading to photoreceptor apoptosis has been postulated but retinal degeneration has also been shown to occur despite G-protein inactivation [43 44]. However, a causal link between opsin mislocalisation and subsequent retinal degeneration has not been proven and it is possible that photoreceptor viability is affected by other molecular pathways unrelated to opsin mislocalisation, which in itself may simply be a marker of ensuing retinal degeneration.

The amino acid sequence of RPGR provides a clue to its function [14]. The main recognisable feature is its RCC1 homology domain that suggests a function as a guanine nucleotide exchange factor for Ran (a Ras-related nuclear protein) and

catalysis of RanGTP [15]. RanGTP serves as an energy source for molecular motors that move cargo through the nuclear pore complex. The resultant high local concentration of RanGTP in the connecting cilium as generated by RPGR could enable a putative RanGTP-dependent process that drives unidirectional movement of opsins across the connecting cilium to the outer segment [39 45].

RPGR **Animal Models**

Two naturally occurring *RPGR* ORF15 mutations in the Siberian husky canine breed result in distinct phenotypes. A 5-nucleotide deletion in *RPGR* ORF15 (del1028-1032) gives rise to a premature stop codon and truncation of 230 residues, resulting in X-linked Progressive Retinal Atrophy 1 (XLPRA1) secondary to loss of RPGR function [46]. This phenotype is characterised by gradual photoreceptor degeneration that is post-developmental in onset, affecting rods more than cones, in keeping with human RP, albeit with slower progression. Optical coherence tomography (OCT) demonstrates normal outer nuclear layer (ONL) thickness up to 28 weeks of age, while at older ages (from 56 weeks) ONL thickness starts to decline in the inferior retina while initially remaining preserved at the visual streak [47]. The second more severe phenotype, XLPRA2, is caused by a 2-nucleotide deletion in ORF15 (del1084-1085), downstream to the first, resulting in frameshift and the inclusion of 34 basic amino acids with truncation of 161 residues [46]. OCT demonstrates a generalised decline in ONL thickness that is worse at the cone-rich central visual streak than the periphery [47].

It has been proposed that the early onset of disease in XLPRA2 from around 5 weeks, with rapid progression affecting both rods and cones, may be caused by a

toxic gain of function from an accumulation of abnormal protein product in the endoplasmic reticulum [40 46]. However, the treatment effect shown after adeno-associated viral (AAV) vector mediated *RPGR* gene transfer in these animals [47] argues against a gain of function mechanism. The finding that two distinct phenotypic expressions of XLPRA are related to the exact nature and position of the ORF15 mutations [46] appears to be confirmed by genotype-phenotype correlations in patients as discussed below [9].

Three mouse models of RPGR deficiency exist. In the first, generated by the deletion of *RPGR* exons 4-6 [39], cone opsin mislocalisation to inner segments, nuclear and synaptic regions was seen and rhodopsin levels were reduced in rods when examined 20 days postnatally. Retinal structure however was comparable to wild-type and electroretinogram (ERG) function was within normal limits despite a lack of RPGR. However, by 6 months, photoreceptor cell loss was apparent [39]. This model demonstrates a slow retinal degeneration, not dissimilar to XLPRA1, and therefore does not emulate the severe degeneration in humans [46]. One of the major shortfalls of murine models to recapitulate human disease is a predominance of rods over cones. In addition, there may not have been a total absence of RPGR protein product as residual RPGR ORF15 isoform was reported to be present in this model [30]. However, two further mouse models, one a naturally occurring 32 base pair duplication in ORF15 [38], the other an engineered deletion of exon 1 [48], show very similar phenotypes to the original knock-out mice. As these models do not appear to have residual RPGR protein, it is unlikely that the putative presence of remaining protein causes the relatively slow rate of degeneration in the murine retina.

RPGR **Clinical Phenotypes**

Disease-causing sequence variants have been identified in *RPGR* in association with a range of phenotypes including rod-cone dystrophy or retinitis pigmentosa (RP), cone dystrophy (COD), cone-rod dystrophy (CORD), macular atrophy, and rarely syndromic XLRP. RP and CORD are the commonest and best described conditions, so genotype-phenotype correlations will be discussed. The vast majority of retinal disease-causing mutations are loss-of-function alleles, with the majority of these being protein truncations in ORF15.

RPGR Retinitis Pigmentosa (Rod-Cone Dystrophy)

XLRP is one of the most severe forms of RP, with nyctalopia in most affected males before ten years of age and progression to legal blindness by the third to fourth decade [49]. Myopia, retinal and electrophysiological abnormalities are often present from childhood [49 50]. Most carrier females are asymptomatic or mildly affected, with a minority of females as severely affected as males [50-52]. A significant proportion of carrier females can be identified on the basis of a tapetal reflex seen clinically and/or with fundus autofluorescence (FAF) imaging, and/or generalised retinal dysfunction on electrophysiological testing.

A parafoveal hyperautofluorescent ring is present in some male patients on FAF imaging [53-55]. There is good correlation between ring radius and pattern ERG P50 amplitude (measure of macular function), indicating greater preservation of function with larger rings; this ring constricts over time and thereby may be a

measure of rate of progression both in the clinic and as an end-point for clinical trials [53-55].

An OCT-based 'transition zone' model has been described with progression from an intact foveal centre to diseased periphery, evidenced first by outer segment shortening, followed by decreased ONL thickness and further outer segment loss, preceding inner segment ellipsoid zone (EZ) band disappearance [56]**.** Annual width decrease of the EZ band was estimated at 248 µm/year in a group of 28 XLRP patients [57]. Functional correlates have been probed, using static perimetry, in 40 patients with *RPGR* XLRP, with demonstration of greatest rate of decline in retinal sensitivity located at the edges of EZ band disappearance [58].

Sharon *et al* [9] screened *RP2* and *RPGR* in 187 unrelated male patients and their affected relatives, and identified disease-causing variants in 16 and 156 patients respectively, with 71% (111/156) of *RPGR* mutations in ORF15. Age-matched patients with *RPGR* ORF15 sequence variants had milder disease compared with patients with *RPGR* exon 1-14 variants, including larger intact visual fields and 30Hz ERG amplitudes, suggesting that the truncated mutant protein is able to perform some function, for example through the intact RCC1-like domain, or that a role exists for constitutive RPGR within ORF15 mutant photoreceptor cells. It was also proposed that for patients harbouring ORF15 variants, disease severity varied according to the predicted length of the encoded abnormal amino acid sequence; with relatively better retinal function associated with longer wild-type ORF15 amino acid sequences secondary to more downstream variants [9]. Moreover, mutations in the first 14 exons that affect both constitutive *RPGR* and the *RPGR* ORF15 isoforms lead to the most severe disease.

Fahim *et al* [59] studied 98 affected males with 44 different *RPGR* mutations. Patients were grouped into 3 categories of disease severity based on ERG and Humphrey visual field findings. In keeping with Sharon *et al* [9], patients with exon 1-14 variants (often predicted null alleles) had more severe disease than patients with ORF15 variants (predicted potentially translatable transcripts); with ORF15 disease being associated with far greater variability in disease severity.

Several studies have identified that ORF15 variants causing RP are far more frequently located towards the 5' end, whereas variants located towards the 3' end of ORF15 more often result in COD/CORD [60-64]. However, there remains significant intra- and inter-familial variability with examples of both RP and CORD within the same families despite the same underlying sequence variant in *RPGR* [61 65 66], suggesting that genetic and/or environmental modifiers are also influencing phenotype.

RPGR Cone and Cone-Rod Dystrophy

Disease-causing sequence variants in *RPGR* are the commonest cause of XLCOD and XLCORD [62]. Multiple studies have reported detailed phenotypic findings in both affected males and carrier females [62-64 67-70]. Onset of central visual loss in affected males ranges from the second to the fourth decade, are often myopic, with significant inter- and intra-familial variability both in terms of onset, rate of progression, and rod involvement. This phenotypic heterogeneity is the hallmark of inherited retinal disease and suggests an important role for genetic modifiers and environmental factors.

In keeping with X-linked inheritance, most carrier females are asymptomatic or mildly affected, with a minority of females as severely affected as males [64]. Variability between and within families is believed to be primarily due to varying degrees of skewed X-inactivation, although other genetic modifiers have been proposed [62 64 67-71].

Parafoveal hyperautofluorescent rings are present in some *RPGR* COD and CORD male patients on FAF imaging and can progressively increase in size over time. In contrast to RP rings, the size of CORD rings is inversely related to pattern ERG P50 amplitude, indicating worse macular cone function with large rings [53 64 72].

To date all reported patients with COD/CORD harbour variants in ORF15 – with ORF15 variants causing COD/CORD more frequently located towards the 3' end of ORF15 compared to those causing RP [60-64].

RPGR Associated Syndromic Ciliopathy

Cilia defects cause a wide range of genetic conditions, collectively called ciliopathies. It is now well established that many important retinal proteins have a role in cilia function and retinal dystrophy represents a common phenotype in the clinical spectrum of disease [73]. Further evidence for RPGR having an important role in cilia function came from genetic studies where sensorineural hearing loss, bronchiectasis and respiratory tract infections were associated with XLRP caused by an *RPGR* mutation [74]. Additional families have been reported with variable penetrance of these phenotypes, confirming further cases of syndromic disease [50 75 76]. Interestingly, mutations causing syndromic XLRP, to date, are restricted to exons 1-14, suggesting mutations in ORF15 may not be a cause of extra-ocular phenotypes.

Therapeutic Options

Docosahexaenoic acid (DHA) and Vitamin A

Lipids make up ~ 25% of photoreceptors' dry weight, with photoreceptor outer segment membranes containing equal amounts of proteins and lipids, with 80% or more of lipid composition arising from phospholipids [77]. In human rod outer segments, 20-30% of fatty acids within phospholipids are made up of docosahexaenoic acid (DHA or 22:6 ω 3) [77]; thereby suggesting an important biochemical role in photoreceptors. DHA and vitamin A are both essential components of the visual cycle. Interphotoreceptor retinoid-binding protein (IRBP) can bind either palmitate or DHA resulting in an alteration in affinity for vitamin A isomers [78]. IRBP when located near the retinal pigment epithelium (RPE) predominantly binds palmitate, creating high affinity for 11-*cis* retinal, which is thereby bound and transported to rod outer segments. High levels of DHA in rod outer segments lead to a swap in IRBP fatty acid binding, with subsequent release of 11-*cis* retinal to the outer segments where it forms rhodopsin. Following phototransduction, all-*trans* retinol in the outer segment is bound to IRBP and brought back to the RPE, where DHA is swapped with palmitate thereby resulting in a release of all-*trans* retinol for 11-*cis* retinal [78].

It has therefore been suggested that a lack of DHA, secondary to outer retinal degeneration, may hinder the release of 11-*cis*-retinal, thus giving rise to the hypothesis that DHA levels around photoreceptor outer segments can be increased (in order to facilitate release of 11-*cis* retinal) with DHA supplements or alternatively by increasing retinal levels of 11-*cis* retinal with vitamin A supplementation [79].

A Cochrane review [80] assessed 3 randomised controlled trials on the effectiveness of vitamin A or DHA in RP, including XLRP [81-83]. No clear evidence of benefit with either vitamin A or DHA supplementation was identified on the basis of visual field or ERG parameters. As a result, high dose vitamin A supplements are not routinely recommended to patients. It is generally accepted that eating a healthy and balanced diet, one that is rich in green vegetables and oily fish that will provide good amounts of lutein and omega-3 is instead likely to be of value.

Neuroprotection

There is evidence from animal studies that ciliary neurotrophic factor (CNTF) delivered either with intravitreal injection of CNTF protein or gene therapy mediated with adeno-associated viral (AAV) vectors exerts a neuroprotective effect on rods, with slowing or halting of retinal degeneration [84]. Recombinant human CNTF has been shown to stimulate cone outer segment regeneration in a rat model of advanced retinal degeneration where rods have already degenerated [85]. In addition, sustained CNTF delivery via implanted devices was shown to preserve cone ERG response and function in the same rat model. [85]

A phase II/III trial has been undertaken of intravitreal implants of encapsulated human retinal pigment epithelium cells engineered to continuously secrete CNTF protein in patients with early (n=68) and late-stage (n=65) RP [86]. Patients were randomly assigned to receive a high- or low-dose implant in 1 eye and sham surgery in the fellow eye. Primary endpoints were change in best-corrected visual acuity at 12 months for late-stage RP and change in visual field sensitivity at 12 months for early RP. Neither study showed therapeutic benefit – with some patients

experiencing loss of retinal sensitivity that was reversible on removal of the implant. However, a pilot study utilising adaptive optics imaging to investigate *in vivo* cone structure in 3 patients with CNTF implants over a 24 month period found that cone density remained stable in eyes with a CNTF implant whereas there was continued cone loss in untreated fellow eyes, suggesting that more sensitive metrics are needed as primary outcome measures in slowly progressive diseases such as RP [87].

Gene Therapy

Successful photoreceptor rescue with *RPGR* ORF15 transgenes has been demonstrated in animal models. Hong *et al* [88] generated a transgenic mouse model that carried mouse *RPGR* ORF15 variant on an *RPGR* null background. The selected *RPGR* ORF15 variant had a 654 base pair deletion within the repetitive purine rich region. Protein expression levels 20% that of wild-type was observed with localisation to the connecting cilia, sufficient for structural and functional rescue of photoreceptors. Another more recent study in *RPGR* null mice has been carried out via subretinally injected AAV vector mediated delivery of two shortened human *RPGR* ORF15 transgenes [89]. The repetitive purine rich region was shortened by 378 base pairs for the first transgene and 942 base pairs for the second transgene. Protein expression followed with both versions of transgene. Appropriate subcellular localisation to the connecting cilia and comparable immunofluorescence signal intensity to wild type was seen with the longer protein, with structural and functional rescue of photoreceptors. A much weaker immunofluorescence signal was however obtained with the shorter gene. A greater efficacy is anticipated with the moderately shortened yet functional version of human *RPGR* ORF15 transgene

compared with the wild-type gene, as the long and repetitive purine rich region present in full length *RPGR* ORF15 is less stable and this may affect the efficacy of gene transfer to photoreceptor cell nuclei. The improved efficacy would be favourable for future human gene therapy trials.

XLPRA1 and XLPRA2 canine models have been successfully rescued with subretinal injection of AAV delivering human *RPGR ORF15* [47]. Post-treatment monitoring with *in vivo* OCT imaging demonstrated a preserved ONL and greater inner segment ellipsoid layer integrity in the retina exposed to vector compared to adjacent un-injected retina, in both XLPRA1 and XLPRA2. These findings were confirmed with histopathology, whereby prevention or reversal of opsin mislocalisation was observed only in the subretinally treated areas. The development of retinal degeneration was prevented with early treatment in XLPRA1, whereas in XLPRA2, due to the earlier onset of this phenotype, intervention during disease progression allowed morphological restoration of remaining photoreceptors [47].

Conclusions

The successful rescue in the aforementioned animal models and the safety and efficacy demonstrated in previous gene therapy trials for Leber Congenital Amaurosis associated with *RPE65* deficiency [90-92] have paved the way for several groups around the world to prepare for Phase I/II gene replacement trials in the near future. However, there is a limiting lack of robust natural history data in large genetically proven groups of patients with XLRP and XLCORD due to *RPGR*. These data are needed in order to design clinical trials of planned gene replacement

therapy. As observed with the CNTF clinical trial, novel outcome metrics are needed in such relatively slowly progressive disease to sensitively detect change in a timely and robust fashion, which may include quantitative retinal imaging with OCT and adaptive optics scanning light ophthalmoscopy. The significant progress made in understanding disease-mechanisms and treatment modalities are exciting and make the aim of future targeted treatments a realistic possibility [93].

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