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# Retinitis pigmentosa caused by mutations in the *RPGR* gene — review of the literature

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## ABSTRACT

Retinitis pigmentosa (RP) is a varied collection of inherited disorders marked by numerous genes, mutations, and clinical manifestations. Progress in the treatment hinges on identifying causative genes and mutations, involving gene discovery and mutation screening for potential gene therapy. Significant advances have been made in detecting RP genes and mutations, with 30–80% detection rates using techniques like next-generation sequencing (NGS), revealing several novel RP genes and clarifying many unresolved cases. However, discrepancies between molecular findings and clinical symptoms often require genetic reevaluation. This review provides a concise overview of the current strategies and challenges in gene discovery and mutation detection in RP. It suggests that these considerations may also be relevant to other inherited retinal diseases. This review examines the *RPGR* gene's pivotal role in X-linked RP (XLRP) and associated retinal dystrophies, focusing on its isoforms' impact on ciliary function and protein trafficking. We discuss the genetic and clinical implications of *RPGR* mutations, particularly novel pathogenic variants, and their genotype-phenotype correlations. Ultimately, this synthesis aims to enhance understanding of *RPGR*'s role in retinal dystrophies, informing future research and potential treatments.

**KEY WORDS:** next-generation sequencing; inherited retinal diseases; genetic screening; *RPGR*, retinitis pigmentosa; genotype-phenotype correlation; *RPGR*-related retinal dystrophies

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## INTRODUCTION

Retinitis pigmentosa (RP) encompasses a varied group of hereditary degenerative disorders marked by the gradual decline in function of rod and cone photoreceptors in the retina. This primarily affects photoreceptor and pigment epithelial functions and leads to retinal degeneration. RP is the most common inherited retinal dystrophy globally, affecting 1 in 4,000 individuals [1].

RP can be inherited in various patterns, including autosomal recessive (50–60% of cases), autosomal dominant (30–40% of cases), and X-linked (5–15% of cases). X-linked RP (XLRP) is one of the most severe forms of RP, and a family history of the condition is present in about 70% of patients [1, 2].

The RP GTPase regulator (*RPGR*) gene, situated on the X chromosome, has emerged as a significant focus in understanding the molecular genetics behind RP and related retinal dystrophies. This gene's mutations are predominantly associated with X-linked forms of retinitis pigmentosa (XLRP) and, to a lesser extent, with cone dystrophy (COD) and cone-rod dystrophy (CORD) [3].

The intricate nature of *RPGR*, characterized by its extensive alternative splicing resulting in multiple isoforms, underscores the complexity of its role in the retina and the diversity of phenotypic expres-

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sions observed in affected individuals. Recent studies have provided substantial insights into the structural and functional facets of RPGR, particularly highlighting the significance of its major isoforms, *RPGRex*1–19, *RPGR* ORF15, and *RPGR*skip14/15, in ciliary genesis, maintenance, and protein trafficking within the retina [4].

The loss of RPGR function leads to disrupted protein transport, affecting photoreceptor viability and causing various forms of retinal dystrophies. The pathogenic variants in *RPGR* have been linked to a range of clinical manifestations, with the type and severity of the disorder often determined by the variant's specific location within the gene [5].

So far, there has been no dedicated screening for disease-causing variants of the *RPGR* gene in the Polish RP patient population. Literature on pathogenic variants within the Polish group of individuals with inherited retinal dystrophies (IRDs) is limited [6–8].

This review aims to consolidate the current understanding of *RPGR*-related RP, delving into the genetic and clinical spectrum associated with its mutations. By examining recent advancements from cohort studies and case reports, including the identification of novel pathogenic variants and the exploration of genotype-phenotype correlations, we endeavor to provide a comprehensive overview of the role of *RPGR* in retinal dystrophies.

## HETEROGENEITY OF PATHOLOGY, CLINICAL MANIFESTATIONS, AND GENETICS OF RP

During the early stage, the primary symptom is night blindness (nyctalopia), which may manifest at various ages, from early childhood to the second decade of life or later. Patients might experience defects in peripheral visual fields under dim light at this stage, but their vision remains normal in daylight conditions. Diagnosing RP in the early stage is challenging, particularly when there is no familial history. Clinical examinations might show normal fundus, optic disc, and color vision, while electroretinogram (ERG) tests are crucial for better understanding the condition.

In the middle stage, patients become aware of the loss of peripheral visual field in daylight conditions, missing objects, or gestures like handshaking. Night blindness becomes more evident, making it difficult to drive at night or walk in dark environments. Dyschromatopsia, or difficulty distinguishing light colors (yellow and blue hues), also appears. Patients may experience photophobia, particularly in diffuse lights, leading to reading problems due to lower visual acuity and a narrow window between too bright and insufficient light. Clinical examination at this stage reveals retinal atrophy, bone-spicule-shaped pigments in the midperiphery, a fairly pale optic disc, and narrowing of retinal vessels [9].

During the end stage, peripheral vision loss severely impacts patients' mobility, making it impossible for them to move from one place to another without assistance. Reading becomes increasingly difficult and ultimately impossible as the central visual field deteriorates. Photophobia intensifies, and clinical examination shows widespread pigment deposits in the macular area, an achromatic optic disc, and thin blood vessels. ERG becomes unrecordable at this stage [10].

RP typically begins with night blindness, followed by a gradual loss of peripheral vision, ultimately leading to central vision loss. However, there is significant variability in age of onset, progression rate, rod versus cone involvement, and the participation of other retinal cells, such as the retinal pigment epithelium (RPE). RP can manifest as non-syndromic, lacking other clinical symptoms, or as syndromic/systemic RP, which may include additional neurosensory disorders, developmental anomalies, or complex clinical phenotypes. Examples of syndromic RP include Usher syndrome, marked by RP and congenital or early-onset deafness, and Bardet-Biedl syndrome (BBS), characterized by RP along with kidney disease, obesity, polydactyly, and developmental delay.

The heterogeneity of RP encompasses genetic, allelic, phenotypic, and clinical dimensions. This extensive diversity can be perplexing for both patients and clinicians, posing challenges in diagnosis. Enhancing the understanding of RP necessitates a more systematic collection of mutation phenotype-genotype data for inherited retinal diseases, similar to the initiatives undertaken by the Leiden Open Variation Database [11].

## OCULAR FINDINGS

Classic fundoscopic manifestations of RP are often characterized by a trio of symptoms: thinning of the retinal vessels, pallid optic nerve head, and intraretinal pigmentation following a bone-spicule pattern. A study found that 94% of the 384 eyes examined exhibited retinal vascular thinning, and 52% showed optic disc pallor [11].

Retinal pigmentary changes arise as melanin from disintegrating retinal pigment epithelial cells relocates to the superficial retina in response to photoreceptor loss [12]. Initially, pigmentary alterations present as a subtle scattering from the mid to outer peripheral retina. Subsequently, "bone spicules" develop across the mid and outer retinal periphery, forming clusters around the retinal vessels [13]. In advanced stages of RP, choriocapillaris atrophy may reveal underlying larger choroidal vessels.

As the condition progresses to moderate or advanced phases, the macula or central retina becomes compromised, leading to retinal atrophy and diminishing visual acuity due to ongoing photoreceptor degeneration [12]. Some individuals may exhibit a central atrophic or bulls-eye lesion.

RP patients might also experience cellophane maculopathy (or "surface wrinkling retinopathy") and foveal cysts, with or without accompanying edema, further diminishing visual acuity beyond that caused by photoreceptor loss. Notably, about half of RP patients develop cataracts, especially posterior subcapsular types [11], with a higher incidence in the autosomal dominant variant [14].

Additional observations in RP include the presence of dust-like pigment granules in the vitreous humor [15] and functional anomalies in refractive error, visual acuity and fields, contrast sensitivity, and color perception.

## GENETICS

RP can present with various inheritance patterns, such as autosomal dominant, autosomal recessive, X-linked, or mitochondrial, and may manifest as either syndromic or non-syndromic [16]. Numerous genes implicated in phototransduction, cellular trafficking, and rhodopsin recycling pathways have been identified [17].

While the impact of these mutations on the functioning of photoreceptors is understood, the exact processes causing their deterioration are still undefined. It's vital to determine and understand the shared pathways of cell death in the varied landscape of RP to create therapies effective across all gene variations causing the disease. This review synthesizes recent studies to identify the cell death routes implicated in RP and how specific mutations trigger these pathways [19].

Different symptoms may arise in various individuals with the same genetic mutation, and distinct mutations can cause the same syndrome [20].

In the last 20 years, significant progress has been made in pinpointing genes linked to inherited retinal diseases like RP, leading to a more complex understanding of the relationship between genes, mutations, and clinical symptoms. This understanding not only deepens our knowledge of vision but also sheds light on retinal disease mechanisms. From a clinical perspective, two crucial questions emerge: the status of mutation identification in patients and the implications for clinical practice. While focused on RP, this discussion is relevant to other inherited eye conditions. RP is characterized by diverse inheritance patterns and genetic causes. A single mutation can manifest differently in individuals (phenotypic pleiotropy), and different mutations can cause the same condition (allelic heterogeneity). The RetNet website provides a comprehensive list of RP-related genes [21].

Determining the exact genetic defect causing RP offers multiple advantages, including verifying RP diagnosis in uncertain situations, predicting the outlook for patients and the risk for relatives, identifying specific RP variants to qualify for clinical trials as targeted therapies emerge, and isolating the root of the disease to deepen knowledge of retinal biology and disease processes. In the United States, non-syndromic RP, which typically presents symptoms confined to the eye, constitutes approximately 65% of all RP cases [20]. The inheritance patterns for these cases are distributed as follows: approximately 30% autosomal dominant, 20% autosomal recessive, 15% X-linked, and 5% recessive early-onset [Leber congenital amaurosis (LCA)]. The remaining 30% are sporadic.

In autosomal dominant RP, there's a 50% chance that an affected individual's children will inherit the condition. For autosomal recessive RP, when both parents are carriers, each child has a 25% chance of being affected. Usually, males are the ones who manifest X-linked RP. However, female carriers of the X-linked RP gene can also show signs of visual impairment [22]. Affected males won't transmit the defective gene to their sons, but all their daughters will inherit the carrier status. If there's no known RP in the family and the abnormal gene remains undetected, the chance of children having RP drops below 5%, except in instances of blood relation (consanguinity) within the family [23].

Beyond standard RP types, syndromic variants affect multiple organs. The most common, Usher syndrome, involves early hearing loss and subsequent RP. Bardet-Biedl syndrome, another prevalent

form, includes extra fingers or toes, obesity, kidney issues, and intellectual delays. Nephronophthisis (NPHP) gene mutations lead to early kidney failure and RP. Through family studies, many genetic regions linked to RP have been discovered, with the first identified mutation in the rhodopsin gene (RHO) on chromosome 3q21.3 in 1989 [24].

In 1990, researchers discovered that a proline-to-histidine change at the 23rd amino acid of rhodopsin, a light-sensitive pigment in rod cell membranes, accounts for 10% of autosomal dominant RP cases among the White population in the United States. The identification of RP-related mutations has accelerated significantly, with over 3000 mutations across approximately 70 genes now recognized [25].

Non-syndromic RP is linked to 71 genes, while syndromic RP involves 66 genes, and LCA is associated with 14 genes. The proteins these genes encode are engaged in various functions, including phototransduction processes, vitamin A metabolism, cytoskeletal components, communication and signaling, RNA splicing, protein transport, and phagocytosis. As of 2007, the three most common genes related to RP, making up about 30% of all cases, are *RHO* (over 26% of autosomal dominant RP cases), *USH2A* (Usherin) (10% of autosomal recessive RP cases and also implicated in both non-syndromic RP and Usher syndrome), and *RPGR*; approximately 75% of X-linked RP [26].

In 2008, another gene, *EYS* — a homolog of Drosophila eyes shut was identified as the gene responsible for autosomal recessive RP at the RP25 locus [27].

This gene is implicated in a substantial number of autosomal recessive RP cases across various global ancestries. *EYS*, the largest eye gene spanning more than 2 million base pairs, is believed to contribute to a protein essential for the structural integrity of the eye's outer segment. Mutations linked to the disease are identified in over 50% of autosomal dominant RP cases, 30% of recessive RP cases, 70% of recessive LCA cases, and nearly 90% of X-linked RP cases [28].

## MOLECULAR GENETICS OF THE *RPGR* GENE

The *RPGR* gene is situated in the Xp11.4 chromosomal region, covering 172 kb and comprising up to 22 exons, depending on the splicing process [29, 30].

The RPGR protein is detected in a range of human tissues, including the lungs, kidneys, testes, brain, and particularly the retina [31]. It is located in the transitional area of primary and motile cilia, as well as in centrosomes and centrioles of cells undergoing division [32]. While its precise function in the retina has yet to be fully understood, the *RPGR* gene is believed to play a vital role in the formation, maintenance, and functionality of cilia, including protein trafficking and organization [17]. The role of *RPGR* as a guanine nucleotide exchange factor (GEF) for small guanine triphosphatases (GTPases) may be essential for transporting substances to the outer segments of photoreceptors [33].

Research indicates that mouse photoreceptor cells can form properly, conduct light signals, and stay alive for the first few months without the RPGR protein. However, over time, the lack of RPGR disrupts the movement of proteins to the photoreceptors' outer segments, and the partial displacement of opsins seems to diminish the survival of these cells [34]. Therefore, *RPGR's* role in ciliary operations doesn't seem to be essential but rather supportive, playing a crucial part in the prolonged preservation of photoreceptors [35].

Due to alternative splicing, over 20 distinct *RPGR* isoforms have been identified [36, 37].

In the retina, three main *RPGR* isoforms are prevalent: *RPGRex*1–19, *RPGR* ORF15, and *RPGR*skip14/15. *RPGRex*1–19 is derived from exons 1–19, *RPGR* ORF15 from exons 1–14 (shared with *RPGRex*1–19) and the additional ORF15 exon, which includes exon 15 and part of intron 15 at the 3' end [38], and *RPGR*skip14/15 is generated through an alternative splicing process [39].

Although the *RPGR* ORF15 isoform has fewer exons than *RPGRex*1–19, its ORF15 exon exceeds the total length of exons 16–19. This exon features a large 1.5 kb sequence of purine-rich repeats and encodes a 560 amino acid protein domain, ending with a sequence of basic amino acids known as the *RPGR*-C2 domain (1071–1152 amino acids). The Glu-Gly region of *RPGR* is similar to the polyglutamated sections of alpha-tubulin [40]. The glutamylation process in *RPGR* ORF15 is regulated by the tubulin-tyrosine ligase-like 5 (TTLL5) enzyme, which is linked to various retinal dystrophies [41].

## RETINAL DYSTROPHIES ASSOCIATED WITH THE *RPGR* GENE

Mutations in the *RPGR* gene can lead to various retinal conditions, such as RP in 70–90% of cases,

cone dystrophy (COD) in about 7%, and cone-rod dystrophy (CORD) in approximately 6–23% [42, 43]. Studies suggest that the specific disorder may depend on the mutation's location: mutations in exons 1–14 and the initial segment of the ORF15 exon are typically associated with RP. In contrast, mutations in the latter part of the ORF15 exon are linked to COD/CORD [44, 45]. The ORF15 exon, which encodes a highly repetitive domain, is considered a mutational hot spot, as most disease-associated variations are truncating [46]. De Silva et al. identified a critical zone of approximately 100 amino acids between these regions where variations can lead to either phenotype [47].

X-linked inheritance is rare in COD/CORD (only 1%) [48], but the *RPGR* gene is responsible for 73% of COD/CORD cases [49]. Primary symptoms include reduced VA, abnormal color vision, central scotoma, and photophobia. These symptoms are associated with variations in all isoforms, though conflicting reports exist regarding the association between the location of the variation within the *RPGR* gene and disease severity. Signs of rod dysfunction may develop as the disease progresses, and patients may also experience night blindness and peripheral VF loss [50].

Unlike RP, symptom onset in COD/CORD occurs later (in the fourth decade) but can progress to blindness relatively quickly by 40–50 years of age [51, 52]. In a study by Nassisi et al., the rate of best-corrected visual acuity (BCVA) decline was assessed at about 7% per year, with most patients reaching a BCVA ≥ 1 logMAR during the fifth decade of life [3].

## CONCLUSIONS

This review emphasizes the significance of the *RPGR* gene in the pathogenesis of RP and related retinal dystrophies. The genetic and phenotypic diversity of RP, especially due to various *RPGR* mutations, presents diagnostic and therapeutic challenges. Understanding the gene's role in ciliary function and photoreceptor maintenance is key to advancing targeted therapies. The severity and progression of *RPGR*-related disorders are mutation-specific, necessitating precise genetic identification for prognosis and treatment planning. Ongoing research and comprehensive genetic screening are essential to improving management and outcomes for individuals with these complex retinal conditions.

### Author contributions

Conceptualization: K.B., K.N., R.R.; data curation: K.B., K.N., R.R.; formal analysis: K.B., K.N., R.R.; investigation: K.B., K.N., R.R.; methodology: K.B., K.N., R.R.; supervision: K.B., K.N., R.R.; writing — original draft preparation: K.B., K.N., R.R.; writing — review & editing: K.B., K.N., R.R. All authors have equally contributed to each stage of the manuscript preparation.

### Conflict of interest

The authors report no competing interests.

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