Review Article

Genetic dissection of non-syndromic retinitis pigmentosa

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Retinitis pigmentosa (RP) belongs to a group of pigmentary retinopathies. It is the most common form of inherited retinal dystrophy, characterized by progressive degradation of photoreceptors that leads to nyctalopia, and ultimately, complete vision loss. RP is distinguished by the continuous retinal degeneration that progresses from the mid-periphery to the central and peripheral retina. RP was first described and named by Franciscus Cornelius Donders in the year 1857. It is one of the leading causes of bilateral blindness in adults, with an incidence of 1 in 3000 people worldwide. In this review, we are going to focus on the genetic heterogeneity of this disease, which is provided by various inheritance patterns, numerosity of variations and inter-/intra-familial variations based upon penetrance and expressivity. Although over 90 genes have been identified in RP patients, the genetic cause of approximately 50% of RP cases remains unknown. Heterogeneity of RP makes it an extremely complicated ocular impairment. It is so complicated that it is known as "fever of unknown origin". For prognosis and proper management of the disease, it is necessary to understand its genetic heterogeneity so that each phenotype related to the various genetic variations could be treated.

Key words: Inherited retinal dystrophy, photoreceptors, retinal degeneration, retinal pigment epithelium, retinitis pigmentosa

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Retinitis pigmentosa (RP, MIM 268000) is a class of inherited retinal dystrophies (IRD) involving continuous degradation of rod and cone photoreceptors that results in nyctalopia (night blindness), and ultimately, vision loss.[1] It is one of the leading causes of bilateral and irreversible blindness in adults.[2] RP is the most common IRD with an incidence of 1 in 3000 people worldwide, but may vary from 1:9000 to 1:750 in various populations.[3,4] Males are affected slightly more often than females due to the X-linked form of the disease occurring more frequently in males. In the case of the Indian population, limited studies are available (only from central and south India). There is a high occurrence of RP in southern India (It was observed at 1 in 1000 in the state of Andhra Pradesh.).[5] In another study, the prevalence was seen at approximately 1 in 930 in urban areas, and 1 in 372 in rural areas.[6] In the case of central India, the occurrence of RP is 1:750 in adults aged 30+ years of the rural population.[7] Its high prevalence makes it the most common form of IRD.[8,9]

Typical signs of RP include retinal pigmentation in the form of bone spicules, vascular attenuation, and waxy pallor of optic disc. These are called as the classic triad of retinitis pigmentosa. For these symptoms, age of onset, progression rate and severity are variable among different patients, which indicates the clinical heterogeneity of the disease. The disease may be early onset (if the signs and symptoms of mid stage of RP are attained and observable at the age of two years) or late onset (if the signs and symptoms of early stage of RP are attained and observable at or after the midlife).[9] The progression rate depends on the age of onset of the symptoms, and remains high and low for early and late onset, respectively. Severity is connected with the Mendelian inheritance type of the disease. At autosomal dominant, RP is least severe, while X-linked RP is the most severe form.[4] Retinal functions which are primarily affected due to RP involves visual field/perimetry, dark adaptation, visual acuity, color vision, and the electrophysiological condition of photoreceptors.[4] Myopia, astigmatism, cataracts, and cystoids macular edema (occurrence increased with age) are some secondary ocular defects that are common in most RP patients. Some patients also have cystoids macular edema.[10]

Clinically, the disease is divided in three main stages: early, middle. and late stage. The disease symptoms become more prevalent from early to late stage. Nyctalopia is the main symptom in the early stage. This nyctalopia is usually avoided by most of the patients until mid or end stage (tunnel vision) because their life quality is not highly affected.[11] At the mid-stage, nyctalopia becomes more effective due to far-peripheral retinal degeneration. Type III (yellow-blue) color blindness is attained along with photophobia.[1] Pigment release from the retinal pigment epithelium (RPE) is also observable at this stage. Accumulation of this pigment occurs in the mid-peripheral region in the form of bone-spicules while other regions look like normal. At this stage, there is the beginning of

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waxy pallor of the optic disc.[10] At the end stage, autonomous moving becomes impossible for the patients because only tunnel vision remains functional at this stage.[1] Cone degeneration at the end stage leads to the loss of visual acuity.[12] Fundus examination reveals that pigment accumulates all over the retina (macula included) at this stage.[10]

RP is an inheritable group of disorders and follows various patterns of inheritance.[13] It is a very complex disease genetically. There are inter- or intra-familial variations related to development, penetrance, and expressivity of the disease.[14] Its complexity can be explained by the various inheritance patterns followed by it, which involve autosomal dominant (AD, 15%–25%), autosomal recessive (AR, 5%–20%), X-linked (XL, 5%–15%), simplex or sporadic (40%–50%), digenic and mitochondrial inheritance (very rare).[10]

Most of the RP–causing genetic variations are associated with the rod photoreceptors and a few with the RPE. The genetic variations lead to rod cell death. Various mechanisms have been identified for the rod cell death. Some of them are apoptosis, phototoxic/photo-oxidative damage, endoplasmic reticulum (ER) stress, defective cilia transport, and defective mRNA processing. Degeneration of rod cells changes the retinal environment, which becomes the cause of the degeneration of cone cells and the RPE.[15]

Clinical, genetic and morphological heterogeneity of RP makes it an extremely complicated ocular impairment.[16,17] It is so complicated that it is known as a "fever of unknown origin".[18] In this review, we are going to discuss the genetic heterogeneity of the disease.

Genetic heterogeneity

RP is an inheritable ocular disease and can be used as a model to study genetic diseases. It is a very complex genetic disease and the complexity is provided by various patterns of disease inheritance, a large number of variations in various genes, and various biological functions in which these genes are involved. Table 1 lists the RP–causing genes are categorized on the basis of their functions. Aside from a large number of variations, there are also complications due to inter- or intra-familial variations based on penetrance and expressivity of the disease symptoms. The genotype–phenotype interrelationship of RP is impossible to explain due to its complex heredity.[1,19] Various biological mechanisms in which RP genes are involved include the cascade of photo-transduction, visual cycle, ciliary structure and transport, OS structure, interphotoreceptor matrix, retinal metabolism, retinal development, retinal homeostasis, transcription and RNA splicing.[4,19]

In most cases, RP is inherited in three patterns: autosomal dominant, autosomal recessive, and X-linked. But rarely, digenic and mitochondrial forms are also found. If there is only one RP patient in a family, even if there is no case in the phylogenetic tree, this form is known as sporadic RP.[17] This also increases the complexity of the genetics of the RP disease.[9] A number of genes have been identified for RP, but all these identified genes cover only 40%–50% of all RP patients, and the rest of the patients do not show any variations in these genes.[20] Table 2 lists all of the mapped (identified and non-identified) genes for RP.

Most of the genetic variations have been shown to cause RP, and most of the genetic variations are limited to photoreceptor cells; the least of these occur in the RPE cells.[19] Various inheritance patterns and the involved genes are described below. Some of these genes show more than one type of inheritance pattern. Such genes are described according to their preference for one pattern (most likely to be followed by them).

Table 1: Genes affecting various biological mechanisms involved in RP.[4]

Biological mechanisms	Associated genes
Photo-transduction cascade	RHO, PDE6A, PDE6B, PDE6G, CNGA1, CNGB1, SAG, GUCA1B
Visual cycle	ABCA4, RDH12, RBP3, CRBP1, RDH11, RLBP1, RDH8, RDH14, DHRS3, DEGS1 LRAT, RGR, RPE65
Ciliary structure and transport	ARL3, RP2, IFT140, IFT172, BBS1, BBS2, TTC8, ARL6, RPGR, SPATA7 AGBL5, ARL2BP, BBS1, C2orf71, C8orf37, CLRN1, FAM161A, FSCN2, KIZ, MAK, OFD1, POMGNT1, RP1, RP1L1, RP2, TOPORS, TULP1, USH2A
Outer-segment structure	FSCN2, PRPH2, ROM1, PROM1, RP1, RP1L1
Inter-photoreceptor matrix	IMPG2, RBP3, EYS
Retinal metabolism	HK1, IDH3A, IDH3B, PANK2
Retinal development	ARHGEF18, C2orf71, FAM161A, IFT140, IFT172, OFD1, SEMA4A, SLC7A14, ZNF408, ZNF513
Retinal homeostasis	BEST1, CA4, CERKL, HGSNAT, KLHL7, MERTK, MVK, REEP6
Gene transcription	CRX, NEUROD1, NR2E3, NRL, SAMD11
RNA splicing	CWC27, DHX38, PRPF3, PRPF31, PRPF4, PRPF6, PRPF8, RP9, SNRNP200
Unknown	ADGRA3, EMC1, KIAA1549, PRCD

Autosomal dominant RP

Autosomal dominant RP (ADRP) covers almost 30%–40% of all RP patients, 38% of which include gene defects disturbing splicing patterns.[17] Uncontrolled splicing may result in various human diseases, but most of such variations are related to ADRP (with unknown reason).[21] More than 20 distinct genes have been shown to cause ADRP, while only some of these cover a pertinent percentage of patients.[1] The causative genes are divided here into two categories: most prevalent genes and rare genes. These are described as follows.

Most prevalent genes

Rhodopsin gene

Rhodopsin (*RHO*), also known as RP4, is the first identified cause of RP.[22,23] The gene spans 5.5 kb of DNA and consists of five exons. It codes for a protein of 348 amino acids called rhodopsin, which makes up more than 90% of the protein content of the rod outer segment (ROS) discs and provides scotopic (low-light) vision.[24,25] It is the most studied G-protein-coupled receptor (GPCR). The characteristic three-dimensional structure of rhodopsin consists of seven

Table 2: Genes associated with non-syndromic RP.[https://sph.uth.edu/retnet/]

Inheritance pattern	Associated genes	
	Non-identified (only mapped)	Identified
ADRP	RP63	ADIPOR1, ARL3, BEST1, CA4, CRX, FSCN2, GUCA1B, HK1, IMPDH1, IMPG1, KIF3B, KLHL7, NR2E3, NRL, PRPF3, PRPF4, PRPF6, PRPF8, PRPF31, PRPH2, RDH12, RHO, ROM1, RP1, RP9, RPE65, SAG, SEMA4A, SNRNP200, SPP2, TOPORS
ARRP	RP22, RP29	ABCA4, AGBL5, AHR, ARHGEF18, ARL6, ARL2BP, BBS1, BBS2, BEST1, C2orf71, C8orf37, CERKL, CLCC1,CLRN1, CNGA1, CNGB1, CRB1, CWC27, CYP4V2, DHDDS, DHX38, EMC1, ENSA, EYS, FAM161A, GPR125, HGSNAT, IDH3B, IFT140, IFT172, IMPG2, KIAA1549, KIZ, LRAT, MAK, MERTK, MVK, NEK2, NEUROD1, NR2E3, NRL, PDE6A, PDE6B, PDE6G, POMGNT1, PRCD, PROM1, PROS1, RBP3, REEP6, RGR, RHO, RLBP1, RP1, RP1L1, RPE65, SAG, SAMD11, SLC7A14, SPATA7, TRNT1, TTC8, TULP1, USH2A, ZNF408, ZNF513
XLRP	RP6, RP24, RP34	OFD1, RP2, RPGR
Digenic		PRPH2, ROM1

transmembrane (TM) helices with an intradiscal N-terminus and a cytoplasmic C-terminus.[26]

RHO variations are known to cover 26.5% of all ADRP cases.[25] Among all the RP patients, 10% of cases resulted from genetic variations in this *RHO* gene. Genetic variations of the *RHO* gene can be inherited in two forms, that is, autosomal dominant and autosomal recessive.[22] In the rhodopsin gene, 150 variations have been identified for RP phenotypes.[25] These variations are spread out over the entire length of the gene.[27] The amino acid positions 135, 190, and 347 are the hot spots for variations in the worldwide population of RP.[28] Variations in the cytoplasmic domain of the gene result in a more severe form of the symptoms in comparison to the intradiscal domain.[25,29] The variation pro347leu in the *RHO* gene results in the most severe form of RP.[30] The pathogenic variations of the rhodopsin gene can be categorized into seven different classes based on their cellular and biochemical characteristics. However, all of these variations lead to a single outcome: the death of rod cells, thereby causing RP. And there are many variations which have not been studied in detail and are unclassified.[19]

The proportion of *RHO* variations in Chinese, Japanese, French, Italian, Belgian, Spanish, and Iranian ADRP patients is 8.9%–16.7%, 11.5%, 18.3%, 16%, 14%, 8%–21%, and 23.8%, respectively.[31,32]

Pre-mRNA processing factor31 gene

The gene pre-mRNA processing factor (*PRPF31*) is located on chromosome 19, spanning 16.3 kb. The association of genetic variants of *PRPF31* with RP was uncovered in 2001 for the first time. It encodes 6 different protein-coding transcripts. The most commonly expressed transcript is made up of 14 exons; 13 are coding while 1 is non-coding. It is the largest transcript and produces a protein of 55 kDa consisting of 499 amino acids. Functional domains of *PRPF31* include the Nop domain, flexible loop, coiled-coil domain and tip. The Nop-domain has the specificity for the U4 binding. The flexible loop protects the RNA from free-radical attack.[33]

The most common splicing factor gene for ADRP is *PRPF31*.[34] Splicing factors are essential for retinal development and maintaining visual function.[35] These factors have been proven to control the splicing process in all kinds of cells, but disease-causing variations in genes encoding these factors are limited to the retina only. High expression of *PRPF31* in the retina tells us about the heavy dependence of the retina on alternative splicing.[34] Being a part of the U4 snRNP, *PRPF31* is essential for the assembly of the U4/U6.U5 tri-snRNP and also for its stability. Genetic variations lead to destabilization of the complex (U4/U6.U5 tri-snRNP), and eventually apoptotic cell death.[36]

In *PRPF31*, a huge number of genetic variations (>100) have been identified which cover 5%–10% of ADRP cases.[37] The most common variations are related to exons 6–10. The disease mechanism behind these variations is haploinsufficiency, which is also responsible for incomplete penetrance of the disease phenotypes, which is the most distinctive feature of the *PRPF31* variations.[33] Reduction in this *PRPF31* protein has been observed to affect the alternative splicing of genes including *RHO*, *ROM1*, *FSCN2* and *GNAT1*, and also, *RHO* is the most affected gene.[35] Patients have been shown to reach complete blindness up to the age of 30.[38]

It is one of the most common causes of ADRP and affects 6% of ADRP cases in the US, 8%–8.9% in the Spanish, French–Canadian, and North American populations, 10%–14.5% in Chinese cohorts, and 10% in the Belgian population.[31,39]

Peripherin2 gene

The Peripherin2 (*PRPH 2*) gene, also known as retinal degeneration slow (*RDS*), is located at position 6p21.1. It consists of three exons which span 26,395bp of DNA.[40] Abnormalities in the *PRPH 2* gene were initially observed to cause retinal degeneration in rats, and was hence named as retinal degeneration slow.[41,42] Variations in this *PRPH 2* gene were observed in the pathogenesis of ADRP in 1991 for the first time.[43] It is one of the most frequent causes of ADRP.[1] Five to nine percent of all ADRP patients are covered by gene defects in *PRPH 2*. Digenic RP can also be seen here when there are variations in both genes (*PRPH 2* and *ROM1*). The human *PRPH 2*/*RDS* gene encodes a glycoprotein of 39 kDa which is called peripherin-2 or retinal degeneration slow. This glycoprotein consists of 346 amino acids and is found in the outer segment of both types of photoreceptor cells (rods and cones) where it controls the discs' structure and functioning by forming complexes with the ROS membrane protein (*ROM1*). Sixty to eighty percent of wild-type peripherin-2 protein is a prerequisite for outer segment disc stabilization.[44]

Peripherin-2 is a member of the tetraspanin family and consists of four helical transmembrane domains (M1–M4) and two intradiscal loops (known as the D1 and D2 loops). The C-terminus region plays a critical role in the process of membrane fusion, which is vital for disc morphogenesis and shedding.[45] It acts as oligomers (composed of dimers) which form tetramers, mediated by the D2 loop.[46] The D2 loop consists of cysteine residues which are important for protein structure. One specific cysteine residue (Cys150) is a prerequisite for the polymerization of tetramers.[47] Tetramers are required for proper targeting of the protein to newly formed outer segment disc membranes. It forms two types of tetramers: homotetramers as well as heterotetrameric complexes with protein *ROM1*.[45]

Most of the *PRPH 2* variations, associated with ADRP, are related to a specific region of the D2 loop (Lys193 to Glu226) and are of missense type. Animal studies show that mutant peripherin/rds leads to the shortening of photoreceptor outer segments which results in the outer segments' disc phagocytosis and thus retinal degeneration.[48] More than 175 variations in the *PRPH 2* gene are known to cause various retinal dystrophies.[49] Genetic variations in this gene are also related to other retinal dystrophies.[50] The frequency of *PRPH 2* variations varies from 0% to 8% in ADRP cases of various populations. Variations in the *PRPH 2* gene in ADRP patients of various cohorts are 0% in Italian, 3.9% in Spanish, 3.5% in Northern American, 14.1% in Japanese, 8% in American and Swedish, 10.3% in French and 4.7% in Belgian.[51–54]

Retinitis pigmentosa1 gene

The retinitis pigmentosa1 gene (*RP1*) is made up of four exons, but only the last three exons are protein-coding.[55] Exon number 4 is the largest one and forms 85% of the coding region of the protein.[56] In 1999, the gene was observed to be involved in ADRP for the first time.[57] It was the fourth gene to be identified for ADRP.[58] It accounts for 5.5% of ADRP cases and 1% of autosomal recessive RP (ARRP) cases.[57]

The gene encodes a protein of 2156 amino acids (240 kDa), which is a photoreceptor-specific microtubule-associated protein.[59] Initially, the protein was named oxygen-regulated protein-1. But now, it is known as retinitis pigmentosa1 due to its involvement in ADRP.[56] It consists of two domains: the DCX domain through which interaction between the protein and the microtubules occurs, and the BIF domain which regulates normal morphogenesis of the photoreceptor.[59] For survival of the photoreceptors, the DCX domain is very essential.[56] The protein is located on the axoneme and the connecting cilium of the photoreceptors (rods and cones) where it regulates the transport of other proteins from photoreceptors' inner segment to the outer segment, maintenance of cilial structure and outer segment disc membranes' stabilization.[59]

RP1 is related to both ADRP (mostly) and ARRP (rarely).[59,60] *RP1*-induced ARRP has more severe disease symptoms than *RP1*-induced ADRP. Animal studies have shown that ADRP causing *RP1* variations works in a dominant-negative way.[61]

Truncating variations are a frequent cause of *RP1*-induced retinitis pigmentosa. In the *RP1* gene, 185 variations have been identified. Out of those, 147 are truncation variations while 38 are of the missense type.[55] Amino acid residues between 500 and 1053 (in exon 4) act as a variational hotspot for ADRP.[60] RP–causing truncating variations in the *RP1* gene have been divided into four classes. Variations of class I occupy the 2nd and 3rd exons and work in a loss-of-function manner. Class II variations are located in the hot spot of *RP1*, which includes the amino acid positions 500–1053 in the 4th exon. These variations cause ADRP due to their dominant negative effect. Class III variations cause loss-of-function, which leads to ARRP. These variations include the amino acid positions 264–499 and 1054–1751 in the 4th exon. Variations of class IV include the variations in the 4th exon which are near the 3′ end.[62] The prevalence of ADRP–causing *RP1* variations in Belgian, Spanish, Italian, French, US, and UK populations is 10.5%, 3.5%, 5%, 5.3%, 7.7% and 8%–10%, respectively.[54]

Inosine Monophosphate Dehydrogenase-1 gene

Inosine monophosphate dehydrogenase-1 (*IMPDH1*) is the fifth most frequent gene responsible for ADRP and account for 2.5% of all the RP cases and 5%–10% of ADRP cases in US and Europe.[63,64] It is located at the position 7q32.1 with 18 exons. Genetic variants are associated with ADRP (mostly) and leber congenital amarousis (LCA, rarely).[65] IMPDH1-associated RP is mostly a severe form of RP with fast-progression and early onset of the disease.

The encoded protein is an isoform of IMPDH expressed in humans. In the retina, it is expressed in the outer nuclear layer, inner segment, and the synaptic terminals of the photoreceptor cells. It acts as a catalyst to synthesize xanthine monophosphate (rate limiting step for guanine nucleotides synthesis). The catalytic region of these IMPDH proteins consists of α/β barrel structure (eight stranded) and this catalytic region is flanked by two cystathionine β-synthase repeats (CBS domains). These proteins act as homotetramers (binding with single stranded nucleic acid) and show association with polyribosomes (through the CBS domain). These interactions are thought to function in replication, transcription, translation and also in metabolism of the nucleic acids.[63]

In humans, the canonical isoform of IMPDH1 consists of 514 amino acid residues. However, two retinal isoforms (splice variants) consist of 546 and 595 amino acids. These isoforms bear similar C-terminal segment, while the isoform with 595 amino acids bears extension at the N-terminal segment.[66]

IMPDH1 is a ubiquitously expressed protein; however, the variations result only in retinal degeneration. ADRP- causing variants localize around the CBS-domain. But these variations don't have any effect on the homotetramer formation or the catalytic activity of the protein. ADRP variants act in gain-of-function or dominant-negative way. It has also been found that these variations result in retinal degeneration by protein misfolding and aggregation.[63] Variations result in changed pool size of the guanine nucleotides and being the highest energy demand, the retina is adversely affected due to this change.[66]

Pre-mRNA processing factor 8 gene

Pre-mRNA processing factor 8 (*PRPF8*) gene is located at 17p13.3 and consists of 43 exons. Of all the spliceosome proteins, *PRPF8* is the most conserved and largest protein with a MW of 220 kDa. It lies in the center of the spliceosome.[67] It is involved in various functions of U5 snRNP, including recognition of branch region and splice site, U4/U6.U5 tri-snRNP assembly and stabilization, exon alignment, and

spliceosomal catalytic core activation.[68] The Jab1/MPN domain regulates the helicase activity of SNRNP200. The entire domain stimulates this activity, while the C-terminal of the domain is involved in the inhibition of this helicase activity.[67]

In spite of ubiquitous expression, variations exclusively result in retinal dysfunctioning. *PRPF8*-mediated RP is a result of ciliary dysfunctioning.[69] Twenty-two variations have been identified in *PRPF8* for RP13, most of which are confined to the terminal exon (Jab1/MPN domain).[68] These transcripts may escape the non-mediated decay (NMD), which lead to the accumulation of these non-functional variant proteins. This results in changed levels of PRPF8 and thus, in retinal dysfunctioning.[70]

It is well known that retinal health depends on the circadian rhythms. In mice models, it has been proven that PRPF8 is involved in proper regulation of the circadian rhythms. And it is possible that misregulation of the circadian rhythms gives rise to retinal diseases by interacting with other environmental factors (bright light, aging, etc).[69]

Nuclear receptor subfamily 2 group E member 3 gene

The Nuclear Receptor subfamily 2 group E member 3 (*NR2E3*) gene is located at the position 15q23, consists of eight exons and spans 7.7 kb of the DNA. It was identified in 1999. Retinal diseases caused by this gene include ADRP, ARRP, enhanced S-cone syndrome, goldmann–favre syndrome and clumped pigmentary retinal degeneration.[71]

The gene encodes for a protein of 45 kDa with 410 amino acid residues which is a photoreceptor specific transcription factor which plays crucial role in rod cells development and maintenance.[71] It promotes rod-specific genes (e.g., RHO) transcription and represses the cone-specific genes by associating with other genes including *CRX*, *NRL* and *NR1D1*. It has the structure of nuclear receptor and involves N-terminal A/B domain (highly variable), C-domain (highly conserved and forms DBD), D-domain (most flexible and also called as hinge domain), and C-terminal E/F domain (conserved secondary structure, also called as LBD). The DBD controls DNA binding and interaction with CRX. And the LBD is involved in the homodimerization which is necessary for the transcriptional repression.[72]

After P23H in *RHO*, G56R in *NR2E3* is the second most common variation causing ADRP.[72] It is responsible for 1%–2%, 3.5%, 1.2%, 3.4% and 1.2% of all ADRP cases in Spanish, American, European and Chinese families, respectively.[73]

Small nuclear ribonucleoprotein U5 subunit 200 (snRNP200) gene

Small nuclear ribonucleoprotein U5 subunit 200 (*snRNP200*) gene is located at 2q11.2 and consists of 45 exons. Spliceosome (pre-mRNA splicing machinery) is a complex made up of protein and RNA subunits. It consists of snRNPs including U1, U2, U4, U5 and U6. And the gene snRNP200 encodes for a U5-specific protein (called as hBrr2, having 2136 amino acid residues) which catalyzes the unwinding (ATP-dependent) of U4/U6 which is crucial for spliceosome activation.[74] The protein has two DExD/H box ATPase domains and a Sec63 domain follows each of them. The codon number 3260 acts as variational hotspot.[75] Variational hotspots for RP are associated with the U4 snRNP binding channel.[76] In a zebrafish model, it has been observed that variants affect this unwinding and result in rod cells demorphogenesis. But the pathogenic mechanism is yet unclear.[74]

In 2009, *snRNP200* was identified as the cause of ADRP (in two Chinese families) for the first time. It accounts for 1.6% of all the ADRP cases.[77] Variant frequency of *snRNP200* for ADRP is 5.8%, 2.3% and 1.5% in Chinese, Spanish and American cohorts, respectively.[31]

Kelch like family member 7 gene

Kelch-like family member 7 (*KLHL7*) gene is located at the chromosomal position 7p15.3. It has 15 exons. It was found to be associated with ADRP in a Scandinavian family.[78] The gene accounts for 1%–2% of ADRP cases.[79]

The gene encodes for two isoforms of protein (with 564 and 586 amino acid residues) having different 5′ exons. Both of these isoforms contain three functional domains: BTB, BACK and Kelch.[79] It is a protein of BTB-Kelch family playing a role in ubiquitinylation. Wide expression of the encoded protein can be seen in rod cells and also in other body tissues including heart, testes, etc. Regulated expression of *KLHL7* is critical for cell survival and homeostasis.[80] Biological function of this protein has not been very clear yet. In the retina, it is thought to stabilize the E3 ligase complex formation.[78] Its E3 activity is exerted by the BTB and BACK domains. BACK domain variations affect its chaperone activity (between E3 ligase and the target substrate), resulting in substrate accumulation and cellular toxicity within the photoreceptor cells.[79]

The variants of *KLHL7* gene are associated with late-onset and slowly progressing ADRP (RP42) and also known to crisponi syndrome or cold-induced sweating syndrome type 1. Its changed expression is involved in the pathogenesis of Parkinson's disease.[78,80]

Cone–Rod Homeobox gene

The cone–rod homeobox (*CRX*) gene is located at 19q13.33. It encodes for a protein containing 299 amino acids which is a homeodomain transcription factor, specific for photoreceptors and controls the expression of other photoreceptor-specific genes. Its expression has been predominantly seen in photoreceptors and pinealocytes. It plays a crucial role in photoreceptor differentiation and maintenance by interacting with some other transcriptional factors (*NRL*, *RAX* and *NR2E3*).[81] The protein structure has three domains: homeodomain (binds with the DNA of other retinal genes), WSP domain, and OTX domain. Missense variations are confined to the homeodomain, while the frameshift variations with premature stop codons are limited to the OTX domain. Both types of mutations work in a dominant-negative way.[82] Genetic variants are involved in various forms of IRDs, which include cone–rod dystrophy, LCA, macular degeneration, and RP. Inheritance pattern for these diseases is AD predominantly.[81]

Pre-mRNA processing factor 3 gene

The pre-mRNA processing factor 3 (*PRPF3*) gene is located at position 1q21.2 and spans 32 kb of the genomic DNA with 16 exons. It encodes for a protein having 683 amino acids and MW of 77 kDa which is localized at the ganglion cells, interneurons and the nuclei of the photoreceptor cells and consists of three domains: PWI, PRP3 and DUF1115.[83] The protein binds to the U6 snRNA and serves as an essential component of the snRNP, U4/U6. It also regulates the stabilization of U4/U6.U5 tri-snRNP

by interacting with other spliceosome proteins (PRPF4 and PRPF6).[76]

Heterozygous variants of *PRPF3* result in RP18 (early-onset form of RP) and accounts for 1.5% of all the ADRP cases. The first ADRP-causing variant of *PRPF3* was reported in 2002. A total of 10 variants have been identified for RP18 in *PRPF3*. Of them, eight missense mutations are clustered at the C-terminal domain (highly conserved and necessary for binding with U4/U6 snRNA and other splicing factors). T94M is the most common variation worldwide.[76] It has been identified in various ADRP populations, including American, Danish, English, Japanese, Korean, Spanish, and Swiss.[83]

TOP1 binding arginine/serine rich protein, E3 ubiquitin ligase gene

TOP1 binding arginine/serine rich protein, E3 ubiquitin ligase (*TOPORS*) gene is located at the position 9p21 with three exons. It spans 13 kb of the genomic DNA and encodes for the protein named as topoisomerase I binding, arginine/serine rich, E3 ubiquitin protein ligase 6.[84] The protein is has 1045 amino acids and is known to interact with p53 and topoisomerase I.[85] It shows ubiquitous expression and serves different functions in different cell types. It is localized to the inner segments of the photoreceptors in the retina. It is a component of sensory cilium of the photoreceptor cells and regulates the primary cilia dependent development and function of the photoreceptors.[84]

It is a ubiquitously expressed gene, but variations result only in ADRP (RP31). Firstly, the ADRP-causing variations in *TOPORS* were identified in 2007 (in a large French-Canadian family and a small German family). It is known to cause 1%û2% of all ADRP cases.[84] Most of the reported variants are located at the last exon and result in premature termination codon (PTC), escaping NMD. These variations work by haploinsufficiency mechanism.[54]

Rare genes

The adiponectin receptor 1 (*ADIPOR1*) gene is located at 1q32.1 and consists of 11 exons. The encoded protein acts as a receptor for the hormone adiponectin and regulates the glucose levels and the catabolism of fatty acids.[86] In the retina, deficiency of ADIPOR1 negatively affects the dietary docosahexaenoic acid (DHA) uptake by photoreceptors. Because this DHA proportion is crucial for the functioning of rhodopsin, ADIPOR1 deficiency results in photoreceptor damage and eventually, visual impairment.[87] Genetic variants may result in isolated as well as syndromic form of RP. First ADRP-causing genetic variant of *ADIPOR1* was identified in a Chinese family in 2016.[86]

The ADP ribosylation factor like GTPase 3 (*ARL3*) gene is located at 10q24.32 and consists of six exons. It encodes for a GTPase protein which shows binding with RP2 and UNC119 and belongs to ADP-ribosylation factor (ARF) family. It plays an important role in protein trafficking to the OS of photoreceptors and crucial for the axoneme formation and ciliogenesis in the retina. p.Tyr90Cys was the first variant identified in *ADIPOR1* for ADRP. The missense variation affects the protein folding and GTP binding/exchange.[88,89]

The bestrophin 1 (*BEST1*) gene is located at 11q12.3 and consists of 14 exons. It encodes for an integral membrane protein (of 585 amino acids) which forms homo-oligomers. The transmembrane proteins function as an anion channel and also regulate the intracellular signaling of calcium within RPE. The gene is associated with five phenotypes: best vitelliform macular dystrophy, autosomal recessive bestrophinopathy, adult-onset vitelliform macular dystrophy, autosomal dominant vitreoretinochoroidopathy, and retinitis pigmentosa. More than 200 genetic variants of *BEST1* have been identified which cause various forms of retinal dystrophies. Association of genetic variants of *BEST1* with RP was first described in 2009.[90]

The carbonic anhydrase (*CA4*) gene is located at 17q23.1 and consists of 13 exons. This is the only RP-causing gene which is expressed outside the retina (in choriocapillaries).[91] It maintains the pH of outer retina which is crucial for normal functioning of the photoreceptors.[92]

It encodes for the protein known as carbonic anhydrase IV. It has been identified for RP (RP17) and it is also involved in glaucoma and stroke.[93] RP-causing genetic variants of *CA4* result in misfolded protein and thus impaired trafficking of the *CA4* to cell surface, which leads to ER-stress induced apoptosis and eventually to retinal degeneration.[94]

The fascin actin-bundling protein 2, retinal (*FSCN2*) gene is a photoreceptor-specific gene located at 17q25 and consists of nine exons. It encodes for a protein of 516 amino acids. The encoded protein is a member of the actin-binding protein family and regulates the morphogenesis of photoreceptors' OS. *FSCN2* is considered as a candidate gene for RP17.[95]

The guanylate cyclase activator 1B (*GUCA1B*) gene is located at 6p21.1. It encodes for the protein called as Guanylate cyclase–activating proteins (GCAPs). GCAPs are involved in the regulation of light sensitivity of the photoreceptor cells and thus involved in their photoresponses. Only one genetic variant (missense variant G157R) of *GUCA1B* has been identified for RP. This variant results in retention of the protein in the IS of photoreceptors which eventually leads to photoreceptor cell death and retinal degeneration.[96]

The hexokinase 1 (*HK1*) gene is located at 10q22.1 and consists of 29 exons. Hexokinases catalyze the first step of glucose metabolism. The encoded protein is ubiquitously expressed and localized to the mitochondrial outer membrane. Genetic variants of HK1 are associated with four phenotypes: non-spherocytic hemolytic anemia, russe type of hereditary motor and sensory neuropathy, RP79 and neurodevelopmental disorder with visual defects and brain anomalies. First case of RP caused by *HK1* variant (E847K) was identified in Japanese patients.[97] The variants may affect the glycolysis or the mitochondrial activity or both.[98]

The interphotoreceptor matrix proteoglycan 1 (IMPG1) gene is located at 6q14.1 and consists of 17 exons. It encodes for a glycoprotein of 150 kDa which constitutes the major component of the IPM of retina. It plays an important role in the maintenance of photoreceptor viability and also in the adhesion of neural retina to RPE. Retinal defects associated with IMPG1 include ADRP and autosomal recessive vitelliform macular dystrophy.[99]

The kinesin family member 3B (*KIF3B*) gene is located at 20q11.21 with a total number of nine exons. It encodes for the protein called as kinesin family member 3B which is involved in the chromosomal movement at the time of mitosis/meiosis. Genetic variants lead to non-syndromic ADRP (RP89), and syndromic ADRP. With the help of functional analysis, it

has been demonstrated that variations increase the length of primary cilia and impair rhodopsin trafficking.[100]

The neural retina leucine zipper (NRL) gene is located at 14q11.2-q12 with seven exons. It is the third gene identified for ADRP. It encodes for a transcription factor which regulates the rod-specific genes and thus plays key role in determination of the rode fate by coordinating with CRX gene.[100] The genetic variants may cause ADRP as well as ARRP. Gain-of-function variants result in ADRP (early onset, RP27), while the loss-of-function variants are known to cause ARRP.[101] All the known variants are located at Pro49, Ser50 and Pro51.[102]

The pre-mRNA processing factor 4 (*PRPF4*) gene is located at 9q32 and consists of 14 exons. The encoded protein is of 60 kDa and make complexes with PPIH and PRPF3. It is a part of both the snRNPs: U4/U6 and U4/U6.U5. Two variants of *PRPF4* (missense variant Arg192His and Pro315Leu) are known to cause RP.[68,103]

The pre-mRNA processing factor 6 (*PRPF6*) gene is located at 20q13.33 and consists of 21 exons. It encodes for a U5 snRNP associated protein of 102 kDa which plays important role in the formation of U4/U6.U5 tri-snRNP by acting as a molecular bridge between di-snRNP and the U5 snRNP. In *PRPF6*, only one variant (c.2185C>T, Arg729Trp) has been identified which causes accumulation of the defective protein in Cajal bodies and thus affecting the snRNP assembly.[68,104]

The retinol dehydrogenase 12 (*RDH12*) gene is located at 14q24.1and consists of seven exons. The encoded protein acts as NADPH-dependent retinal reductase to generate all-*trans*-retinol from all-*trans*-retinal (before transport to RPE) in the photoreceptor cells.[105,106] Genetic variants result in RP, LCA, early-onset retinal degeneration, and Stargardt disease.[107] It is responsible for 3.4%–10.5% of all the LCA cases.[105] Pathogenic genetic variations differ for various ethnic backgrounds.[107]

The retinal outer segment membrane protein 1 (*ROM1*) gene is located at 11q12.3 and consists of three exons. It is a homolog of the gene *PRPH 2*, and both of these genes are essential for the morphogenesis of OS discs (maintain the rim region of discs and also regulate the size of discs). Both of these proteins can homo- or hetero-dimerize for proper functioning.[108] The gene shows digenic inheritance for RP with *PRPH 2*. It acts as a modifier gene for which *PRPH 2* acts as a target.[109]

The RP9 pre-mRNA splicing factor gene (*RP9*) gene is located at 7p14.3 with seven exons. The encoded protein, called as RP9 or PAP1, is a non-snRNP splicing factor and acts as a target and partner of Pim-1 kinase.[68] Genetic variants result in ADRP (RP9) and also concentric RP.[110]

The semaphoring 4A (*SEMA4A*) gene is located at 1q22 and consists of 18 exons. The encoded protein is a transmembrane protein and belongs to the semaphorin family of proteins. It plays an important role in transmembrane ligand for the receptor of photoreceptor cells. It is expressed in the eye and brain. Genetic variants result in ADRP (RP35) and cone-rod dystrophy (CORD).[111] Some genetic variants affect the protein localization or ER stress, while others do not follow this mechanism of pathogenesis.[112]

The secreted phosphoprotein 2 (*SPP2*) gene is located at 2q37.2 with 10 exons. It spans 27 kb on the genomic DNA and encodes for a secreted phosphoprotein (secreted phosphoprotein 2), member of the cystetin superfamily. Dominant negative variations lead to toxicity of the photoreceptors and RPE and eventually, to retinal degeneration due to accumulation of the protein.[113]

Autosomal recessive retinitis pigmentosa

Autosomal Recessive Retinitis Pigmentosa (ARRP) covers 50%–60% of all RP patients, and consanguinity is the main cause of autosomal recessive diseases.[38] More than 40 genes are known to cause ARRP, but only a few genes are responsible for high percentages. All other genes are rare (≤1% of cases).[1] These genes are described as follows.

Most prevalent genes

Usherin gene

The **usherin (*USH2A*)** gene is located at 1q41. It spans 800 kb on the genomic DNA with 73 exons (exon 71 is cochlea-specific). It is the most prevalent gene for isolated ARRP as well as syndromic ARRP. It is responsible for 8%–9% of all the ARRP cases.[114,115]

It encodes for Usherin protein. The protein plays an important role in the development of cochlear hair cells and in photoreceptor maintenance. It is expressed in the retina (inner segments of the photoreceptors) and supportive tissue of the inner ear.[116] It has 48 domains, of which 10 are laminin epidermal growth factor-like (LE) domains, 2 are laminin G-like domains, 35 are fibronectin type III (FN3) domains, and 1 is cysteine-rich domain.

Alternative splicing results in two isoforms: isoform a (short) and isoform b (long). Isoform a is of 5 kb with 21 exons and encodes for 170 kDa protein. Isoform b is of 15 kb and encodes for 600 kDa protein.[115] The long isoform is expressed in predominantly adult retina (photoreceptors).[117]

Genetic variations result in two phenotypes: non-syndromic RP and Usher syndrome type 2a.[116] More than 1100 pathogenic variants of *USH2A* gene are known, including missense, nonsense, splicing, deletions, insertions, indels, and large rearrangement.[118] Insertion variants cause the most severe form of ARRP followed by splicing and missense variants.[116]

ATP-binding cassette, sub-family A, member 4 gene

The **ATP-binding cassette, sub-family A, member 4 (*ABCA4*)** gene is located at 1p22.1 and consists of 50 exons. The encoded protein consists of 2773 amino acids. It is expressed in the outer segments of the photoreceptor cells and plays an important role in cleansing of the intermediate metabolites of visual cycle. Dysfunctioning of ABCA4 affects this cleansing function and results in cytotoxicity to the RPE and eventually, dysfunctioning of RPE and photoreceptor cells.[119]

The gene was identified in 1997 for the first time as a cause of Stargardt disease.[119] It is the most common cause of IRD in Poland. It is known as the most common cause of Stargardt disease 1 and is also responsible for RP, cone-rod dystrophy, and age-related macular degeneration.[120] Of them, ARRP (RP19) has the most severe phenotype and affects both types of photoreceptor cells.[121] In *ABCA4*, a total number of 1513 variants have been identified.[120] Sixty-one percent of total variants are of missense type, while 23% are truncating. Every nation of Europe has a specific most common variant with

higher frequency than any of the other nations; for example, C.768G>T in Netherlands, p.[Leu541Pro; Alal038Val] in Germany, Arg1129Leu in Spain, and p.[Gly863Ala, Gly863del] in Western/Northern Europe. p.(Gly1961Glu) is the most frequent pathogenic variant of *ABCA4* and originated from Eastern Africa (identified in 10% of Somalis). However, it has spread all over the world due to population migration.[122]

Retinal pigment epithelium 65 gene

The human **retinal pigment epithelium 65 (*RPE65*)** gene is localized at 1p31 and spans 20 kb of the DNA. It consists of 14 exons which code for a protein of 533 amino acids called the retinal pigment epithelium-specific 65 kDa protein. The protein has two forms: one is a membrane-bound form called mRPE65 and the other is the soluble form called sRPE65.[123] It is expressed in the cells of RPE for the metabolism of vitamin A. It acts as an enzyme (isomerase) to convert vitamin A (all trans retinyl ester) into 11 cis retinol, and this 11 cis retinol is oxidized to the visual chromophore (11 cis retinal), which plays a vital role in the formation of light sensitive pigments (to drive the phototransduction) of the photoreceptors.[124] The protein is also important for proper localization and survival of the cone opsin.[120]

Five percent of all RP cases are caused by genetic defects in the RPE cells, with this *RPE65* gene accounting for 50% of them.[125] Variations of *RPE65* lead to photoreceptor degeneration and result in RP (mostly ARRP, rarely ADRP) and LCA. *RPE65*-related IRDs show a very early age of onset (from birth to five years) and the patients attain complete vision loss (legal blindness) by the fourth decade of their life. The gene accounts for 0.6%–6% of RP and 3%–16% of LCA cases in various cohorts. More than 300 variations have been identified in this gene, most of which are point variations.[123]

Phosphodiesterase 6 gene complex

The **phosphodiesterase 6 gene complex (*PDE6*-complex)** is a regulator of cGMP concentration in the cytoplasm of photoreceptors. It plays an important role in the visual phototransduction cascade.[120] This complex is made up of heterotetramers having two catalytic and two inhibitory subunits in both types of photoreceptors (rods and cones). In the rod photoreceptors, catalytic subunits are alpha (*PDE6A*) and beta (*PDE6B*) and two gamma (*PDE6G*) subunits act as inhibitory subunits. In the case of the cone photoreceptors, two alpha (*PDE6C*) subunits form the catalytic core, and the inhibitory core is formed by two beta (*PDE6H*) subunits.[126,127]

Variations in the rod-specific *PDE6* gene family result in ARRP, while variants in the cone-specific *PDE6* gene family cause achromatopsia. Of all the cases of ARRP, 8% resulted from variations in the rod-specific *PDE6* gene family.[128] But, variations in only the genes encoding for *PDE6A* and *PDE6B* subunits are responsible for a substantial proportion of ARRP cases.[127]

In case of the visual phototransduction cascade of rod cells, photoexcited rhodopsin activates transducin which, in turn, results in the release of the inhibitory subunit of the *PDE6*-complex. This results in activation of the catalytic subunits of the *PDE6*-complex (PDE6α and β) which hydrolyze the cGMP, leading to membrane hyperpolarization (to convert the light into the nerve impulses). Variations cause permanent opening of the cation-channels (cGMP-gated) of rod photoreceptors' membrane, allowing entry of extracellular ions into the cells in excess amounts. All this finally results in apoptotic cell death of rod cells.[129]

Phosphodiesterase 6A gene

The **phosphodiesterase 6A (*PDE6A*)** gene is located at position 5q32 and spans 87kb of DNA. It is composed of 22 exons encoding a protein of 860 amino acids.[130,131] It was the 7th locus to be identified for RP and responsible for 4% of all ARRP cases with a severe disease.[132,133] ARRP-causing variations in this gene were identified in 1995 for the first time.[133]

Up to now, 40 variations in this gene have been reported as pathogenic, and most of them (65%) are point variations.[130] The *PDE6A* gene accounts for 3%–4% of all ARRP patients in North America, while rare cases of *PDE6A*-related RP are found in populations in Spain, Japan, and United Kingdom.[131] Contribution of ARRP-causing *PDE6A* variants in Pakistani, French, German, and Israeli populations is 2%, 2%, 1.6%, and 1%, respectively.[132]

Phosphodiesterase 6B gene

The **phosphodiesterase 6B (*PDE6B*)** gene, encoding the beta subunit of the *PDE6*-complex, is located at position 4p16.3 and spans 45 MB of DNA. It consists of 22 exons, which encode a protein of 854 amino acids.[126,134] It was the first gene to be identified for ARRP. ARRP-causing variations were identified in 1993 for the first time.[129] It is related to a severe form of RP with an early age of disease onset. Five to eight percent of all ARRP cases are caused by genetic defects in this gene.[135]

Cyclic nucleotide gated channel subunit alpha 1 gene

The **cyclic nucleotide gated channel subunit alpha 1 (*CNGA1*)** gene is located at 4p12 and consists of 11 exons. It is expressed in the rod cells predominantly and involved in the formation of outer segments of the rod cells. The gene encodes for the protein called as cyclic nucleotide gated channel subunit alpha 1 (cGMP-binding channels in the transmembrane of the rod photoreceptors).[136] The cyclic nucleotide-gated (CNG) channels play a key role in the structural and functional maintenance of the photoreceptors. The protein has four functional domains: P-helix, selectivity filter, C-linker, cyclic nucleotide-binding domain, and C-terminal coiled-coil domain.[137]

It causes RP49, which is an early-onset and a severe form of RP.[138] ARRP-causing genetic variants of the *CNGA1* gene were identified in 1995 for the first time. It is responsible for 2%–5% of RP cases worldwide (except Asian population).[136,137] It has relatively high prevalence in Asian populations (7.6% in Chinese population and 5.1% in the Japanese population) and considered as the most prevalent RP- causing gene in Japanese patients.[138,139] A total of 39 variations have been identified in this gene, of which 28 are missense or nonsense, 10 are small deletions, and 1 is splicing substitution.[137]

Retinitis pigmentosa 25 gene

The gene **retinitis pigmentosa 25 (*RP25*)** is located at 6q12. It consists of 46 exons and spans 2 MB of the genomic DNA, being the largest gene in the human eye.[140] Its abundant expression can be seen in the retina with localization in the photoreceptors' outer segments, where it plays a vital role in the formation of photoreceptors and their structural integrity (stability of ciliary axoneme).[141] Variations lead to a severe type of ARRP with an early age of disease onset.[142]

The human *RP25* protein is also called as *EYS* because it shows homology to a protein called Drosophila eyes shut (spacemaker), which is responsible for the development of photoreceptors and eye-morphology in insects.[141] The protein has a signal peptide at the N-terminal position, EGF-like domains, coiled coil domains, and Laminin G-like domains interspersed with repeats of EGF-like domains at the C-terminal. Four isoforms of the protein are known to be expressed in the human retina. The amino acids in isoforms 1, 2, 3, and 4 are 3144, 619, 594, and 3165, respectively.[143]

In case of *RP25* gene, truncating variations are the most common disease-causing variations.[142] Four hundred forty-nine variations have been identified in the *RP25* gene up to now, out of which 219 variations are point variations, 184 are deletions and insertions, 39 are splicing variations, 4 variations are regulatory, and 3 variations are complex rearrangements.[144] A large number of disease-causing variations are found close to the C-terminal region of the protein.[142] The prevalence of *RP25* variations in RP patients from Spain, France, the United Kingdom, China, Germany, Korea, Israel, the Netherlands, and Northern Ireland is 15.9%, 12%, 11%, 10%, 9.1%, 7%, and 0%, respectively. In the case of the Japanese, it is the most common cause of IRD. It accounts for 51% of Japanese RP patients.[145]

Crumbs cell polarity complex component 1 gene

The **crumbs cell polarity complex component 1 (*CRB1*)** gene is located at 1q31.3. It consists of 12 exons and spans 210 kb of the genomic DNA. It uses alternative exons and has 12 transcripts. Major transcripts expressed in the retina include CRB1-A and CRB1-B. CRB1-A consists of 1406 amino acids with EGF-like domains (19) and laminin G domains (3), And also a signal peptide sequence. This transcript is expressed in the muller cells and is predominant in the developing retina. CRB1-B consists of 1003 amino acids. It is expressed in the photoreceptor cells and predominant in the adult retina.[146]

The gene encodes for a protein named as Crumbs homologue 1 (CRB1) which is related to the CRB complex and plays an important role in retinal development.[146] The encoded protein is localized to the inner segments of photoreceptors and shows similarity to the Drosophila Crumbs protein. It is a transmembrane protein and plays a key role in the structure, function and development of the retina.[147]

CRB1-associated diseases include RP12, LCA, and maculopathy.[147] It is responsible for 17% of LCA cases in Spain.[148] Most of the RP-causing variants are of missense type. The variants affect retinal development and photoreceptor signaling. A total number of 457 pathogenic variations (333 missense/nonsense, 86 small insertion/deletions, 28 splice variants, 9 large insertion/deletions, and 1 regulatory substitution) have been identified in *CRB1*.[146] Most of the variations are found in exons 9 (41%) and 7 (27%).[149]

Ceramide kinase like gene

The **ceramide kinase-like (CERKL)** gene is located at 2q31-32 and spans 12 kb on the genomic DNA with 14 exons.[150] It has a complex expression due to alternative splicing (>20 transcripts expressing in various tissues).[151] Its expression has been identified in various body tissues (brain, kidney, and lung) with the highest expression in the retina (four isoforms, having 419, 463, 532 and 558 amino acids are known to be expressed in the retina).[152,153] It is expressed mostly in the photoreceptors and the retinal ganglion cells. It acts in multiple pathways and provides protection to the photoreceptor cells against oxidative stress. There are studies on the expression of genetic variants of *CERKL* also in RPE, but its function in the RPE cells is unknown.[151]

The protein shows 29% similarity with ceramide kinase. But, kinase activity is not reported for it.[154] It consists of three domains: diacylglycerol kinase (DAGK) domain, Pleckstrin homology (PH) domain, and ATP-binding domain. It also consists of two signals, that is, nuclear localization and nuclear export. These signals are involved in the nuclear-cytoplasm trafficking.[152]

It is known to cause ARRP (RP26) and also CORD.[151] It was identified first in a Spanish family having RP and was considered as one of the most prevalent genes for ARRP or CORD in the Spanish cohort.[152,155] In *CERKL*, 39 variants have been identified for IRDs and p.Arg257Stop is the most prevalent variant of *CERKL*.[150,156] Variants result in increased oxidative stress and eventually lead to retinal degeneration.[151]

S-antigen visual arrestin gene

S-antigen visual arrestin (*SAG*) gene is located at 2q37.1 with 21 exons and encodes for the protein S-arrestin or S-antigen, which is a soluble protein of photoreceptors, and is involved in phototransduction-cascade desensitization (recovery phase).[157]

It is involved in the pathogenesis of RP47 and Oguchi disease. Coexistence of Oguchi disease and RP has also been reported in the same family and also in the same individual. Variants are known to cause ARRP in Japanese people and ADRP in Hispanic families. The genetic variant p.Cys147Phe is responsible for 36% of ADRP cases in the Hispanic cohort.[158]

Rare genes

The **adhesion G protein-coupled receptor A3 (*ADGRA3*/*GPR125*)** gene is located at 4p15.2 and consists of 21 exons. The encoded protein is a G protein-coupled receptor. The gene is involved in the pathogenesis of ARRP.[159]

The **AGBL carboxypeptidase 5 (*AGBL5*)** gene is located at 2p23.3 and consists of 18 exons. It encodes for a metallocarboxypeptidase which catalyzes protein deglutamylation during posttranslational modification of the tubulins. The gene is involved in the pathogenesis of RP75.[160,161]

The **aryl hydrocarbon receptor (*AHR*)** gene is located at 7p21.1 with 11 exons. It encodes for a transcription factor and is involved in the pathogenesis of RP85.[162]

The **Rho/Rac guanine nucleotide exchange factor 18 (*ARHGEF18*)** gene is located at 19p13.2 with 35 exons. The encoded protein is a component of tight and adherence junctions and is involved in the development and functioning of the retina. It is involved in the pathogenesis of RP78.[163]

The **ADP ribosylation factor like GTPase 6 (*ARL6*)** gene is located at 3q11.2 with 14 exons. The encoded protein belongs to the ARF-family of GTP-binding proteins and mediates intracellular trafficking. It is associated with phenotypes including Bardet–Biedl syndrome and RP55.[164,165]

The **ADP ribosylation factor like GTPase 2 binding protein (*ARL2BP*)** gene is located at 16q13 and consists of six

exons. The encoded protein is a GTPase and shows binding with ARL2. It is involved in trafficking of ciliary proteins. Genetic variants have been identified for ARRP.[3,166]

The **Bardet–Biedl syndrome 1 (*BBS1*)** gene is located at 11q13.2 with 17 exons. The encoded protein plays a role in eye development. Genetic variants are known to cause ARRP and Bardet–Biedl syndrome.[167]

The **Bardet–Biedl syndrome 2 (*BBS2*)** gene is located at 16q13 with 18 exons. The encoded protein is involved in intracellular trafficking. Genetic variants lead to Bardet–Biedl syndrome and RP74 (Moroccan Jewish and Ashkenazi Jewish families).[168]

The **cilia and flagella associated protein 418 (*CFAP418*/*C8orf37*)** gene is located at 8q22.1 with six exons. Genetic variants are known to cause Bardet–Biedl syndrome 21, cone-rod dystrophy 16, and RP64.[169,170]

The **chloride channel CLIC like 1 (*CLCC1*)** gene is located at 1p13.3 with 15 exons. The encoded protein enables the chloride channel activity. The genetic variants are known to cause RP32.[171]

The **clarin-1 (*CLRN1*)** gene is located at 3q25.1 and having six exons. The encoded protein is involved in photoreceptor synapses. The genetic variants lead to RP61 and Usher syndrome type III. The RP-causing variants have been identified in Pakistani families.[172]

The **cyclic nucleotide gated channel subunit beta 1 (*CNGB1*)** gene is located at 16q21 and consists of 34 exons. The encoded protein regulates the ion flow into outer segments of rod photoreceptors. Genetic variants cause RP45 which was identified in French patients of RP.[173]

The **CWC27 spliceosome associated cyclophilin (*CWC27*)** gene is located at 5q12.3 with 19 exons. It encodes for a protein involved in protein peptidyl-prolyl isomerization and is known to cause isolated and syndromic forms of RP.[174]

The **cytochrome P450 4V2 (*CYP4V2*)** gene is located at 4q35.1-q35.2 with 11 exons. The encoded protein is involved in the oxidation of various metabolic substrates. Genetic variants lead to Bietti crystalline corneoretinal dystrophy and ARRP, and shows founder effect in Asian population.[175]

The **dehydrodolichyl diphosphate synthase (*DHDDS*)** gene is located at 1p36.11 with nine exons. The encoded protein is involved in the *cis*-prenyl chain elongation. The gene is involved in the pathogenesis of congenital disorder of glycosylation, type 1bb, developmental delay and seizures with or without movement abnormalities and RP59. Single variant causing RP59 has been identified in American and Israeli families.[176]

The **DEAH (Asp-Glu-Ala-His) box polypeptide 38 (*DHX38*)** gene is located at 16q22.2 and consists of 28 exons. The encoded protein is an ATPase catalyzing the second step of the splicing process. The genetic variants lead to RP84 and have been identified in Pakistani patients.[177]

The **ER membrane protein complex subunit 1 (*EMC1*)** gene is located at 1p36.13 and consists of 24 exons. The encoded protein is a subunit of EMC with unknown function. The genetic variants lead to ARRP and have been identified in patients from Saudi Arabia.[159]

The **endosulfine alpha (*ENSA*)** gene is located at 1q21.3 with six exons. It encodes for an endogenous ligand for sulfonylurea receptor 1 which regulates KATP channels. Genetic variants are known to cause RP.[178]

The FAM161 Centrosomal Protein A (FAM161 Centrosomal Protein A) gene is located at 2p15 having 11 exons. The encoded protein is involved in the development of retinal progenitors. The genetic variants lead to RP28 and have been identified in Indian, Israeli, Palestinian, and German families.[179]

The **heparan-alpha-glucosaminide N-acetyltransferase (*HGSNAT*)** gene is located at 8p11.21-p11.1 and consists of 20 exons. The encoded enzyme, also known as N-acetyltransferase, is involved in acetylation of heparin sulphate in lysosomes. Genetic variants result in RP73 and Sanfilippo syndrome. C. RP73 was identified in 6 members of Ashkenazi Jewish and Dutch families.[180]

The **isocitrate dehydrogenase (NAD(+)) 3 non-catalytic subunit beta (*IDH3B*)** gene is located at 20p13 and consists of 14 exons. The encoded protein plays a critical role in the Kreb's cycle. The genetic variants result in RP46 and have been identified in patients from North America and Mexico.[181]

The intraflagellar transport 140 (*IFT140*) gene is located at 16p13.3 with 40 exons. The encoded protein is a subunit of intraflagellar transport (IFT) complex A and involved in the primary cilia activities of the photoreceptors. The genetic variants result in RP80, recessive Mainzer–Saldino syndrome and also recessive LCA.[182]

The **intraflagellar transport 172 (*IFT172*)** gene is located at 2p23.3 and has 52 exons. The encoded protein is a subunit of IFT-B and plays a critical role in intraflagellar transport. The genetic variants are associated with Bardet–Biedl syndrome 20, retinitis pigmentosa 71, and short-rib thoracic dysplasia 10 with or without polydactyly.[183]

The **interphotoreceptor matrix proteoglycan-2 (*IMPG2*)** gene is located at 3q12.3 with 19 exons. The encoded protein is a proteoglycan and plays a key role in organizing the interphotoreceptor mix (IPM) for proper maintenance of the outer segments of photoreceptors. Genetic variants result in RP56 and Macular dystrophy, vitelliform, 5. RP variants have been identified in Pakistani, Dutch, Italian and Netherland patients.[184]

The ***KIAA1549*** gene is located at 7q34 with 21 exons. The encoded protein may be involved in retina-soecific function. Genetic variants are known to cause RP86.[185]

The **kizuna centrosomal (*KIZ*)** protein is located at 20p11.23 with 15 exons. The encoded protein plays role in the connecting cilia of photoreceptors and the variation cause RP69.[186]

The **lecithin retinol acyltransferase (*LRAT*)** gene is located at 4q32.1 with four exons. The encoded protein catalyzes the esterification step in the metabolism of vitamin A in the visual system. Genetic variants result in LCA 14 and juvenile RP.[187]

The **male germ cell associated kinase (*MAK*)** gene is located at 6p24.2 with 20 exons. The encoded protein is a kinase playing an important role in cell cycle regulation. The genetic variants result in RP62 which has been identified in Dutch, Italian, Israeli, and Palestinian patients.[188]

The MER proto-oncogene, tyrosine kinase (*MERTK*) gene is located at 2q13 with 19 exons. It encodes for a transmembrane protein involved in the recycling of OS of photoreceptor cells. It is involved in the pathogenesis of RP38. A founder variation accounts for 30% of RP cases in Faroe Islands.[189]

The **mevalonate kinase (*MVK*)** gene is located at 12q24.11 with 13 exons. Genetic variants are associated with the phenotypes including Hyper-IgD syndrome, Mevalonic aciduria, Porokeratosis 3, multiple types and RP.[190]

The **NIMA related kinase 2 (*NEK2*)** gene is located at 1q32.3 with nine exons. It encodes for a ciliary-associated protein that regulated mitosis. It is involved in the pathogenesis of RP67.[191]

The **neuronal differentiation 1 (*NEUROD1*)** gene is located at 2q31.3 and consists of four exons. The gene encodes for a transcription factor which is involved in the neurogenesis. Genetic variants result in syndromic disease with neonatal diabetes, systematic neurological abnormalities, early-onset retinal dystrophy, and ARRP.[192]

The **photoreceptor cilium actin regulator (*PCARE*)** gene is located at 2p23.2 and has two exons. The encoded protein is a ciliary and actin-associated protein involved in photoreceptor function. Genetic variants lead to RP54 and have been identified in various populations with high frequency in Swiss population.[193]

The **phosphodiesterase 6G (*PDE6G*)** gene is located at 17q25.3 and consists of six exons. It encodes for the γ subunit of the cGMP phosphodiesterase which acts as a key enzyme-complex involved in phototransduction. A splice-site variant has been identified for early-onset ARRP (RP57) in an Arab Israel family.[194]

The **protein O-linked mannose N-acetylglucosaminyltransferase 1 (beta 1,2-) (*POMGNT1*)** gene is located at 1p34.1 with 25 exons. The gene encodes for a transmembrane protein which mediates the O-mannosyl glycosylation. It is associated with the phenotypes including muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 3; muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 3; muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 3; and RP76.[195]

The **progressive rod-cone degeneration (*PRCD*)** gene is located at 17q25.1 with eight exons. The encoded protein's function is unknown, but the variants cause RP36. RP-causing variants have been identified in Muslim Arab patients.[196,197]

The **prominin 1 (*PROM1*)** gene is located at 4p15.32 with 35 exons. The encoded protein is involved in the photoreceptor disc membrane morphogenesis. Genetic variants result in various phenotypes including Stargardt disease 4, retinal macular dystrophy 2, cone-rod dystrophy 12 and RP41. The RP-causing variants were identified in Pakistani families.[198,199]

The **protein S (*PROS1*)** gene is located at 3q11.1 with 16 exons. It encodes for plasma protein involved in anticoagulation and also involved in the pathogenesis of RP.[200]

The **retinol binding protein 3 (*RBP3*)** gene is located at 10q11.22 and consists of four exons. It encodes for a glycoprotein that plays a critical role in the transport of retinoids between photoreceptors and RPE. Genetic variations are associated with RP66 (identified in an Italian family) and retinal dystrophy with high myopia.[201,202]

The **receptor accessory protein 6 (*REEP6*)** gene is located at 19p13.3 with six exons. The encoded protein regulates the structure of ER and is involved in the pathogenesis of RP77.[203]

The **retinal G protein-coupled receptor (*RGR*)** gene is located at 10q23.1 and has nine exons. The encoded protein is involved in isomerization (from all-trans-retinal to 11-cis-retinal). The genetic variants lead to the pathogenesis of RP44 and choroidal sclerosis.[204,205]

The **retinaldehyde binding protein 1 (*RLBP1*)** gene is located at 15q26.1 and consists of nine exons. The encoded protein is water-soluble and acts as a functional component of visual cycle. The genetic variants are associated with Bothnia retinal dystrophy, severe RP, fundus albipunctatus, and retinitis punctata albescens.[206,207]

The **RP1 like 1 (*RP1L1*)** gene is located at 8p23.1 with four exons. It encodes for a retina-specific protein involved in microtubule polymerization. The genetic variants are known to cause occult macular dystrophy and RP88.[208,209]

The **sterile alpha motif domain containing 11 (*SAMD11*)** gene is located at 1p36.33 with 15 exons and is known to cause RP.[210]

The **solute carrier family 7 member 14 (*SLC7A14*)** gene is located at 3q26.2 with eight exons. The gene encodes for a transporter protein which is involved in the lysosomal uptake of the cationic amino acids. The genetic variants were identified in Chinese patients with RP68.[211]

The **spermatogenesis associated 7 (*SPATA7*)** gene is located at 14q31.3 with 16 exons. The genetic variants result in LCA, RP, juvenile RP, and CORD. RP-causing variants have been identified in Portuguese and French-Canadian patients.[212,213]

The **tRNA nucleotidyl transferase 1 (*TRNT1*) gene** is located at 3p26.2 and consists of 11 exons. It encodes for a CCA-adding enzyme. The genetic variants result in sideroblastic anemia with immunodeficiency, fevers and developmental delay (SIFD), SIFD with RP, and non-syndromic RP.[214]

The **tetratricopeptide repeat domain 8 (*TTC8*)** gene is located at 14q31.3 with 18 exons. The encoded protein is involved in the cilia formation. The genetic variants result in RP51 and BBS8. RP-causing variants have been identified in North Indian and Pakistani families.[215]

The **TUB like protein 1 (*TULP1*)** gene is located at 6p21.31 with 15 exons. The encoded protein is involved in the physiology (protein trafficking) of the photoreceptor cells. Genetic variations lead to LCA and RP14.[216,217]

The **zinc finger protein 408 (*ZNF408*)** gene is located at 11p11.2 with five exons. The encoded protein is a member of the zinc finger transcription factors involved in retinal vasculogenesis. The genetic variants lead to exudative vitreoretinopathy 6 and RP72. RP-causing variants were identified in Spanish families.[218,219]

The **zinc finger protein 513 (*ZNF513*)** gene is located at 2p23.3 with five exons. The encoded protein acts as a transcriptional

Table 3: Summary of genes involved in the pathogenesis of non-syndromic retinitis pigmentosa. (source adapted from https://sph.uth.edu/retnet/)

Gene (Symbol/OMIM)	Chromosomal Location	Inheritance pattern	Protein	Function
ATP-binding cassette, sub-family A, member 4 (ABCA4/601691)	1p22.1	AR	ATP-binding cassette transporter - retinal	Transport of an essential molecule (or ion) either into or out of photoreceptors
Adiponectin receptor 1 (ADIPOR1/607945)	1q32.1	AD, AR	Adiponectin receptor 1	Receptor for adiponectin, a hormone secreted by adipocytes
AGBL carboxypeptidase 5 (AGBL5/615900)	2p23.3	AR	ATP/GTP binding protein-like 5	Dual-functional deglutamylase that can remove glutamate residues from both carboxyl termini and side chains of protein substrates
Aryl hydrocarbon receptor (AHR/600253)	7p21.1	AR	Aryl hydrocarbon receptor	Regulation of developmental pathways and biological responses to xeno- and phytobiotics
Rho/Rac guanine nucleotide exchange factor 18 (ARHGEF18/616432)	19p13.2	AR	Rho/Rac guanine nucleotide exchange factor 18	Regulation of a wide spectrum of cellular functions including cytoskeletal rearrangements, gene transcription, cell growth and motility
ADP ribosylation factor like GTPase 3 (ARL3/604695)	10q24.32	AD, AR	ADP ribosylation factor like GTPase 3	Interacts with the RP2 protein and regulates trafficking of prenylated proteins and ciliogenesis in the rod outer segment
ADP ribosylation factor like GTPase 6 (ARL6/608845)	3q11.2	AR	ADP-ribosylation factor-like 6	Ciliary function
ADP ribosylation factor like GTPase 2 binding protein (ARL2BP)	16q13.3	AR	ADP-ribosylation factor-like 2 binding protein	Trafficking of ciliary proteins and factors
Bardet-Biedl syndrome 1 (BBS1/209900)	11q13.2	AR	Bardet–Biedl syndrome 1	Ciliary trafficking
Bardet-Biedl syndrome 2 (BBS2/606151)	16q13	AR	Bardet–Biedl syndrome 2	Cilia formation and function
Bestrophin 1 (BEST1/607854)	11q12.3	AD, AR	Bestrophin 1	Transmembrane oligomeric chloride channel
Chromosome 2 open reading frame 71 (C2orf71/613425)	2p23.2	AR	Photoreceptor cilium actin regulator	Regulation of initial development of OS disks
Chromosome 8 open reading frame 37 (C8orf37/614477)	8q22.1	AR	Chromosome 8 open reading frame 37	Maintenance of physiological levels of OS membrane proteins
Carbonic anhydrase 4 (CA4/114760)	17q23.2	AD	Carbonic anhydrase IV	CO_2 and bicarbonate transport
Ceramide kinase like (CERKL/608381)	2q31.3	AR	Ceramide kinase like protein	Regulation of mitochondrial biology and metabolism
Chloride channel CLIC like 1 (CLCC1/617539)	1p13.3	AR	Chloride intracellular ion channel (CLIC)-like protein 1	Maintenance of normal retinal structure and function
Clarin 1 (CLRN1/606397)	3q25.1	AR	Clarin-1	Role in hair cell and photoreceptor synapses
Cyclic nucleotide gated channel subunit alpha 1 (CNGA1/123825)	4p12	AR	Rod cGMP-gated channel alpha subunit	Phototransduction and formation of the structure of rod photoreceptor OS
Cyclic nucleotide gated channel subunit beta 1 (CNGB1/600724)	16q21	AR	Rod cGMP-gated channel beta subunit	Regulation of ion flow into the rod photoreceptor OS
Crumbs cell polarity complex component 1 (CRB1/604210)	1q31.3	AD, AR	Crumbs homolog 1	Retinal development and cell-cell interactions and cell polarity
Cone-rod homeobox (CRX/602225)	19q13.33	AD	Cone-rod otx-like photoreceptor homeobox transcription factor	Differentiation and maintenance of photoreceptor cells

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Table 3: Contd...

Gene (Symbol/OMIM)	Chromosomal Location	Inheritance pattern	Protein	Function
CWC27 spliceosome associated cyclophilin (CWC27/617170)	5q12.3	AR	Spliceosome-associated cyclophilin	
Cytochrome P450 family 4 subfamily V member 2 (CYP4V2/608614)	4q35.2	AR	cytochrome P450 4V2	Fatty acid and steroid metabolism
Dehydrodolichyl diphosphate synthase subunit (DHDDS/608172)	1p36.11	AD, AR	Dehydrodolichyl diphosphate synthetase	An enzyme in the dolichol synthesis pathway
DEAH-box helicase 38 (DHX38/605584)	16q22.2	AR	DEAH (Asp-Glu-Ala-His) box polypeptide 38	Pre-RNA splicing
ER membrane protein complex subunit 1 (EMC1/616846)	1p36.13	AR	ER membrane protein complex subunit 1	
Endosulfine alpha (ENSA/603061)	1q21.3	AR	Endosulfine alpha protein	Regulation of cell cycle progression
Eyes shut homolog (EYS/602772)	6q12	AR	Eyes shut/spacemaker (Drosophila) homolog	Formation of photoreceptors and their structural integrity (stability of ciliary axoneme)
FAM161 centrosomal protein A (FAM161A/613596)	2p15	AR	family with sequence similarity 161 member A	
Fascin actin-bundling protein 2, retinal (FSCN2/607643)	17q25.3	AD	retinal fascin homolog 2, actin bundling protein	Photoreceptor-specific paralog of fascin which crosslinks and bundles f-actin
G protein-coupled receptor 125 (GPR125/612303)	4p15.2	AR	G protein-coupled receptor 125	
Guanylate cyclase activator 1B (GUCA1B/602275)	6p21.1	AD	guanylate cyclase activating protein 1B	Recovery of phototransduction
Heparan-alpha-glucosaminide N-acetyltransferase (HGSNAT/610453)	8p11.21-p11.1	AR	Heparan-alpha-glucosaminide N-acetyltransferase	Catalyzes the only synthetic reaction known to occur in the lysosome
Hexokinase 1 (HK1/142600)	10q22.1	AD, AR	Hexokinase 1	Catalyzes phosphorylation of glucose to glucose-6-phosphate
Isocitrate dehydrogenase (NAD(+)) 3 non-catalytic subunit beta (IDH3B/604526)	20p13	AR	NAD(+)-specific isocitrate dehydrogenase 3 beta	Catalyzes conversion of isocitrate to α-ketogluterate in the citric acid cycle (Krebs cycle)
Intraflagellar transport 140 (IFT140/614620)	16p13.3	AR	Intraflagellar transport 140 Chlamydomonas homolog protein	Activity of primary cilia including photoreceptor cilia
Intraflagellar transport 172 (IFT172/607386)	2p33.3	AR	Intraflagellar transport protein 172	Intraflagellar transport
Inosine monophosphate dehydrogenase 1 (IMPDH1/146690)	7q32.1	AD	Inosine monophosphate dehydrogenase 1	Catalyzes the rate-limiting step in de novo guanine synthesis
Interphotoreceptor matrix proteoglycan 1 (IMPG1/602870)	6q14.1	AD, AR	Interphotoreceptor matrix proteoglycan 1	Component of the photoreceptor extracellular matrix
Interphotoreceptor matrix proteoglycan 2 (IMPG2/607056)	3q12.3	AD, AR	Interphotoreceptor matrix proteoglycan 2	Component of the retinal intercellular matrix
KIAA1549 (KIAA1549/613344)	7q34	AR	KIAA1549 protein	Plays a role in photoreceptor function
Kinesin family member 3B (KIF3B/603754)	20q11.21	AD	Kinesin family member 3B	Chromosome movement and microtubule activity
Kelch like family member 7 (KLHL7/611119)	7p15.3	AD, AR	Kelch-like 7 protein (Drosophila)	Plays a role in the ubiquitin-proteasome pathway leading to protein degradation

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Table 3: Contd...

Gene (Symbol/OMIM)	Chromosomal Location	Inheritance pattern	Protein	Function
Kizuna centrosomal protein (KIZ/615757)	20p11.23	AR	Kizuna centrosomal protein	Stabilizes centrosomes
Lecithin retinol acyltransferase (LRAT/604863)	4q32.1	AR	Lecithin retinol acyltransferase	Catalyzes first step in visual cycle transforming vitamin A into 11-cis-retinol
Male germ cell associated kinase (MAK/154235)	6p24.2	AR	Male germ-cell associated kinase	Regulation of retinal cilium and spermatogenesis
MER proto-oncogene, tyrosine kinase (MERTK/604705)	2q13	AR	C-mer protooncogene receptor tyrosine kinase	Internalization of the photoreceptor outer segment (POS) prior to phagocytosis in RPE
Mevalonate kinase (MVK/251170)	12q24.11	AD, AR	mevalonate kinase	Isoprenoid pathway
NIMA related kinase 2 (NEK2/604047)	1q32.3	AR	NIMA (never in mitosis gene A)-related kinase 2	Ciliary-associated protein involved in cell division
Neuronal differentiation 1 (NEUROD1/601724)	2q31.3	AR	Neuronal differentiation protein 1	Maintenance of adult photoreceptors
Nuclear receptor subfamily 2 group E member 3 (NR2E3/604485)	15q23	AD, AR	Nuclear receptor subfamily 2 group E3	Ligand-dependent transcription factor
Neural retina leucine zipper (NRL/162080)	14q11.2	AD	Neural retina lucine zipper	Retinal transcription factor which interacts with CRX, promotes transcription of rhodopsin and other retinal genes, and is required for rod photoreceptor development
OFD1 centriole and centriolar satellite protein (OFD1/300170)	Xp22.2	XLD, XLR	Oral-facial-digital syndrome 1 protein	Centrosomal protein which interacts with other ciliopathy-associated proteins
Phosphodiesterase 6A (PDE6A/180071)	5q33.1	AR	cGMP phosphodiesterase alpha subunit	Visual phototransduction cascade
Phosphodiesterase 6B (PDE6B/180072)	4p16.3	AD, AR	Rod cGMP phosphodiesterase beta subunit	Visual phototransduction cascade
Phosphodiesterase 6G (PDE6G/180073)	17q25.3	AR	Phosphodiesterase 6G cGMP-specific rod gamma	Visual phototransduction cascade
Protein O-linked mannose N-acetylglucosaminyltransferase 1 (beta 1,2-) (POMGNT1/606822)	1p34.1	AR	O-linked acetylglucosaminyltransferase 1 (beta 1,2-)	O-mannosylation glycosylation pathway
Photoreceptor disc component (PRCD/610598)	17q25.1	AR	Progressive rod-cone degeneration protein	
Pre-mRNA processing factor 3 (PRPF3/607301)	1q21.2	AD	Pre-mRNA processing factor 3	Ubiquitously-expressed member of the U4/U6-U5 tri-snRNP particle complex
Pre-mRNA processing factor 4 (PRPF4/607795)	9q32	AD	Pre-mRNA processing factor 4	A member of the U4/U6-U5 splice complex
Pre-mRNA processing factor 6 (PRPF6/613979)	20q13.33	AD	Pre-mRNA processing factor 6	Ubiquitously-expressed member of the U4/U6-U5 tri-snrnp particle complex
Pre-mRNA processing factor 8 (PRPF8/607300)	17p13.3	AD	Pre-mRNA processing factor 8	Ubiquitously-expressed member of the U4/U6-U5 tri-snrnp particle complex
Pre-mRNA processing factor 31 (PRPF31/606419)	19q13.42	AD	Pre-mRNA processing factor 31	Assembly and stabilization of U4/U6•U5 tri-snrnp
Peripherin 2 (PRPH2/179605)	6p21.1	AD, AR	Peripherin 2	Discs' structure and functioning
Prominin 1 (PROM1/604365)	4p15.32	AD, AR	Prominin 1	5-transmembrane glycoprotein associated with plasma membrane evaginations in rod outer segments

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Table 3: Contd...

Gene (Symbol/OMIM)	Chromosomal Location	Inheritance pattern	Protein	Function
Protein S (PROS1/176880)	3q11.1	AD, AR	Vitamin K–dependent protein S	Anti-coagulant action
Retinol binding protein 3 (RBP3/180290)	10q11.22	AR	Retinol binding protein 3, interstitial	Transfer of retinol between the pigment epithelium and retina during the visual cycle
Retinol dehydrogenase 12 (RDH12/608830)	14q24.1	AD, AR	Retinol dehydrogenase 12	Involved in visual cycle and has unusual dual specificity for all-trans-retinols and cis-retinols
Receptor accessory protein 6 (REEP6/609346)	19p13.3	AR	Receptor accessory protein 6 (receptor expression enhancer protein 6)	Involved in endoplasmic reticulum function and protein transport
Retinal G protein coupled receptor (RGR/600342)	10q23.1	AD, AR	RPE-retinal G protein-coupled receptor	Rod visual cycle
Rhodopsin (RHO/180380)	3q22.1	AD, AR	Rhodopsin	Scotopic vision
Retinaldehyde binding protein 1 (RLBP1/180090)	15q26.1	AD, AR	Retinaldehyde-binding protein 1	
Retinal outer segment membrane protein 1 (ROM1/1807221)	11q12.3	AD, AR	Retinal outer segment membrane protein 1	
RP1 axonemal microtubule associated (RP1/180100)	8q12.1	AD, AR	RP1 protein	Regulates the transport of other proteins from photoreceptors' inner segment to the outer segment, maintenance of cilial structure and outer segment disc membranes' stabilization
RP2 activator of ARL3 GTPase (RP2/312600)	Xp11.23	XL	Retinitis pigmentosa 2 (X-linked)	Trafficking of the membrane proteins
RP1 like 1 (RP1L1/608581)	8p23.1	AD, AR	Retinitis pigmentosa 1-like protein 1	Interact with photoreceptor connecting cilia
RP9 pre-mRNA splicing factor (RP9/180104)	7p14.3	AD	RP9 protein or PIM1-kinase associated protein 1	Pre-mRNA splicing
retinoid isomerohydrolase RPE65 (RPE65/180069)	1p31.2	AD, AR	Retinal pigment epithelium-specific 65 kD protein	Production of 11-cis-vitamin A
Retinitis pigmentosa GTPase regulator (RPGR/310612)	Xp11.4	XL	Retinitis pigmentosa GTPase regulator	Proper organization of microtubule and trafficking of ciliary proteins
S-antigen visual arrestin (SAG/181031)	2q37.1	AD, AR	Arrestin (s-antigen)	
Sterile alpha motif domain containing 11 (SAMD11/616765)	1p36.33	AR	Sterile alpha motif domain containing 11 protein	Signal transduction and regulation of transcription
Semaphorin 4A (SEMA4A/607292)	1q22	AD, AR	Semaphorin 4A	Transmembrane semaphorin (also called semaphorin B) which enhances T-cell activation
Solute carrier family 7 member 14 (SLC7A14/615720)	3q26.2	AR	Solute carrier family 7 member 14	Cationic transporter protein with an unknown ligand
Small nuclear ribonucleoprotein U5 subunit 200 (SNRNP200/601664)	2q11.2	AD	Small nuclear ribonucleoprotein 200kDa (U5)	
Spermatogenesis associated 7 (SPATA7/609868)	14q31.3	AR	Spermatogenesis associated protein 7	
Secreted phosphoprotein 2 (SPP2/602637)	2q37.1	AD	Secreted phosphoprotein 2	
tRNA nucleotidyl transferase 1 (TRNT1/612907)	3p26.2	AR	CCA adding tRNA nucleotidyl transferase 1	tRNA function and protein synthesis
TOP1 binding arginine/serine	9p21.1	AD	topoisomerase I binding	

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Table 3: Contd...

Gene (Symbol/OMIM)	Chromosomal Location	Inheritance pattern	Protein	Function
rich protein, E3 ubiquitin ligase (TOPORS/609507)			arginine/serine rich protein	
Tetratricopeptide repeat domain 8 (TTC8/608132)	14q32.11	AR	tetratricopeptide repeat domain 8	Basal body - ciliary function
TUB like protein 1 (TULP1/602280)	6p21.31	AR	Tubby-like protein 1	Transport of rhodopsin from inner to outer segment
Usherin (USH2A/276901)	1q41	AR	Usherin	
Zinc finger protein 408 (ZNF408/616454)	11p11.2	AD, AR	Zinc finger protein 408	
Zinc finger protein 513 (ZNF513/613598)	2p23.3	AR	Zinc finger protein 513	

Gene (Symbol/OMIM)	Mutation type	Protein change		Disease phenotypes	References
		Structural	Functional		
ATP-binding cassette, sub-family A, member 4 (ABCA4/601691)	Missense, nonsense, insertion, deletion, complex rearrangement	Misfolding	Mislocalization	RP19; Stargardt disease, juvenile and late onset; macular dystrophy; fundus flavimaculatus; cone-rod dystrophy	Huang *et al.*, 2018[121]; Wiszniewski *et al.*, 2005[235]
Adiponectin receptor 1 (ADIPOR1/607945)	Missense	Misfolding	Mislocalization	RP; Bardet–Biedl like syndrome	Zhang *et al.*, 2016[86]
AGBL carboxypeptidase 5 (AGBL5/615900)	Nonsense, missense	Nonsense mediated decay of transcript protein destabilization	Loss of function, interaction with ligands, or other proteins	RP75	Astuti *et al.*, 2016[161]
Aryl hydrocarbon receptor (AHR/600253)	Splice-site variant	Truncated protein	Loss of transcriptional activity	RP85	Zhou *et al.*, 2018[162]
Rho/Rac guanine nucleotide exchange factor 18 (ARHGEF18/616432)	Deletion, missense, nonsense	Truncated protein		RP78	Arno *et al.*, 2017[163]
ADP ribosylation factor like GTPase 3 (ARL3/604695)	Missense, nonsense, insertion, deletion, regulatory substitution	Misfolding	Protein-protein interaction, calcium-binding	RP83; Joubert syndrome 35; cone-rod dystrophy	Fu *et al.*, 2021[88]; Strom *et al.*, 2021[89]
ADP ribosylation factor like GTPase 6 (ARL6/608845)	Nonsense, missense	Misfolding	Disruption of activation of BBSome	RP55; Bardet–Biedl syndrome	Singh *et al.*, 2020[236] Chandrasekar *et al.*, 2018[165]; Pretorius *et al.*, 2011[237]
ADP ribosylation factor like GTPase 2 binding protein (ARL2BP)	Missense, splice-site variants	Abnormal splicing	Reduced binding to ARL2, mislocalization		Fiorentino *et al.*, 2018[3]; Davidson *et al.*, 2013[166]
Bardet-Biedl syndrome 1 (BBS1/209900)	Missense	Splicing defect		RP; Bardet–Biedl syndrome	Fadaie *et al.*, 2016[167]
Bardet-Biedl syndrome 2 (BBS2/606151)	Missense, nonsense			RP74; Bardet–Biedl syndrome	Xu *et al.*, 2015[238]
Bestrophin 1 (BEST1/607854)	Missense, nonsense, frameshift		Ca^{+2} signaling	RP50; macular dystrophy, best type; vitreoretinochoroidopathy; bestrophinopathy	Hartzell *et al.*, 2008[239]
Chromosome 2 open reading frame 71 (C2orf71/613425)	Nonsense, missense		Reduced protein stability	RP54	Nishimura *et al.*, 2010[240]

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Table 3: Contd...

Gene (Symbol/OMIM)	Mutation type	Protein change		Disease phenotypes	References
		Structural	Functional		
Chromosome 8 open reading frame 37 (C8orf37/614477)	Missense, splice-site, nonsense	Truncated protein		RP64; cone-rod dystrophy; Bardet–Biedl syndrome	Estrada-Cuzcano *et al.*, 2012[170]; Chen *et al.*, 2018[169]
Carbonic anhydrase 4 (CA4/114760)	Substitutions	Misfolding	Mislocalization	RP17	Tian *et al.*, 2010[241]; Datta, R., 2010[94]
Ceramide kinase like (CERKL/608381)	Nonsense, missense, splicing, frameshift	Truncated protein		RP26; cone-rod dystrophy with inner retinopathy	Nadeem *et al.*, 2020[242]; Downes *et al.*, 2020[150]
Chloride channel CLIC like 1 (CLCC1/617539)	Missense	Misfolding	Decreased channel activity	RP32	Li *et al.*, 2018[171]
Clarin 1 (CLRN1/606397)	Missense	Truncated protein,	Mislocalization, nonfunctional protein	RP61; usher syndrome	Isosomppi *et al.*, 2009[243]
Cyclic nucleotide gated channel subunit alpha 1 (CNGA1/123825)	Missense, nonsense, deletion, splice-site variants		Nonfunctional protein	RP49	Wang *et al.*, 2016[244]; Saito *et al.*, 2021[137]
Cyclic nucleotide gated channel subunit beta 1 (CNGB1/600724)	Missense, nonsense, splicing, insertion, deletion, duplication, indels			RP45	Nassisi *et al.*, 2021[245]
Crumbs cell polarity complex component 1 (CRB1/604210)	Missense, nonsense, insertion, deletion, splice variants	Truncated protein, misfolding, disruption of disulphide bridges	Altered hydrophobicity and chargeability, impaired protein-protein interactionand calcium-binding activity	RP12; retinitis pigmentosa with para-arteriolar preservation of the RPE; leber congenital amaurosis; pigmented paravenous chorioretinal atrophy	Mairot *et al.*, 2021[146];Guo *et al.*, 2019[246]; Lu *et al.*, 2016[247]; Beryozkin *et al.*, 2013[179]
Cone-rod homeobox (CRX/602225)	Missense, nonsense, deletion, insertion, indels	Truncatede protein	Impaired DNA-binding and loss of transactivation activity	Cone-rod dystrophy; recessive, and de novo Leber congenital amaurosis	Tran and Chen 2014[248]
CWC27 spliceosome associated cyclophilin (CWC27/617170)	Frameshift, splicing, stop-gain	Truncated protein		Retinitis pigmentosa and skeletal anomalies	Xu *et al.*, 2017[174]
Cytochrome P450 family 4 subfamily V member 2 (CYP4V2/608614)	Splice-site variant	Impaired splicing		Bietti crystalline corneoretinal dystrophy	Wang *et al.*, 2012[175]
Dehydrodolichyl diphosphate synthase subunit (DHDDS/608172)	Missense			RP59; congenital disorder of glycosylation, type 1bb; developmental delay and seizures with or without movement abnormalities	Brandwine *et al.*, 2021[176]
DEAH-box helicase 38 (DHX38/605584)	Missense	Misfolding	Altered splicing activity	RP84; macular coloboma	Latif *et al.*, 2018[177]
ER membrane protein complex subunit 1 (EMC1/616846)	Missense, splicing variants	Truncated protein			Cabet *et al.*, 2020[249]
Endosulfine alpha (ENSA/603061)	Deletion	Truncated protein			Yi *et al.*, 2020[178]

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Table 3: Contd...

Gene (Symbol/OMIM)	Mutation type	Protein change		Disease phenotypes	References
		Structural	Functional		
Eyes shut homolog (EYS/602772)	Missense, nonsense, rearrangements, deletions, insertions, splice-site variants, complex rearrangements	Truncated protein		RP25; cone-rod dystrophy and macular dystrophy	Cundy *et al.*, 2021[144]; Garcia-Delgado *et al.*, 2021[142]
FAM161 centrosomal protein A (FAM161A/613596)	Frameshift	Truncated protein		RP28	Shen *et al.*, 2021[250]
Fascin actin-bundling protein 2, retinal (FSCN2/607643)	Deletion	Truncated protein		RP30; macular dystrophy	Liu *et al.*, 2018[251]
G protein-coupled receptor 125 (GPR125/612303)	Missense	Truncated protein			Abu-Safieh *et al.*, 2013[159]
Guanylate cyclase activator 1B (GUCA1B/602275)	Missense		Mislocalization	RP48; macular dystrophy	Avesani *et al.*, 2021[96]
Heparan-alpha-glucosaminide N-acetyltransferase (HGSNAT/610453)	Missense, nonsense, deletion, insertion, frameshift, splice-site variant	Nonsense-mediated decay of mRNA, misfolding, truncated protein	Lack of enzymatic activity	RP73; mucopolysaccharidosis	Martins *et al.*, 2019[252]; Haer-Wigman *et al.*, 2015[180]
Hexokinase 1 (HK1/142600)	Missense			RP79; non-spherocytic hemolytic anemia; hereditary neuropathy (Russe type)	Kubota *et al.*, 2020[97]
Isocitrate dehydrogenase (NAD(+)) 3 non-catalytic subunit beta (IDH3B/604526)	Missense, deletion	Truncated protein		RP46	Hartong *et al.*, 2008[253]
Intraflagellar transport 140 (IFT140/614620)	Missense, frameshift	Nonsense-mediated decay of mRNA		RP80; mainzer-saldino syndrome; Leber congenital amaurosis	Xu *et al.*, 2015[182]
Intraflagellar transport 172 (IFT172/607386)	Missense, insertion, splice-site variant	Missplicing,	Modification or disruption of the protein function	RP71; Bardet–Biedl syndrome	Bujakowska *et al.*, 2015[183]
Inosine monophosphate dehydrogenase 1 (IMPDH1/146690)	Deletion, missense,	Misfolding		RP10; Leber congenital amaurosis	Jin *et al.*, 2014[254]
Interphotoreceptor matrix proteoglycan 1 (IMPG1/602870)	Splice-site variant			RP91; macular dystrophy, vitelliform	Olivier *et al.*, 2021[99]
Interphotoreceptor matrix proteoglycan 2 (IMPG2/607056)	Nonsense, missense, deletion	Truncated protein		RP56; macular dystrophy, vitelliform	van Huet *et al.*, 2014[255]
KIAA1549 (KIAA1549/613344)	Deletion	Nonsense mediated decay of mRNA		RP86	de Bruijn *et al.*, 2018[185]
Kinesin family member 3B (KIF3B/603754)	Missense			RP89; retinitis pigmentosa, syndromic	Cogne *et al.*, 2020[100]
Kelch like family member 7 (KLHL7/611119)	Missense		Attenuation of enzymatic (ligase activity)	RP42; PERCHING syndrome	Kim *et al.*, 2017[80]
Kizuna centrosomal protein (KIZ/615757)	Nonsense, deletion	Nonsense-mediated	Loss of function	RP69	El Shamieh *et al.*, 2014[186]

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Gene (Symbol/OMIM)	Mutation type	Protein change		Disease phenotypes	References
		Structural	Functional		
		decay of mRNA, truncated protein			
Lecithin retinol acyltransferase (LRAT/604863)	Deletion	Nonsense-mediated decay of mRNA		Leber congenital amaurosis	Koster *et al.*, 2021[187]
Male germ cell associated kinase (MAK/154235)	Alu insertion, missense	Truncated protein	Loss of kinase activity	RP62	Cho *et al.*, 2020[256]; Ozgül *et al.*, 2011[257]
MER proto-oncogene, tyrosine kinase (MERTK/604705)	Missense, nonsense, splite-site variants, deletion, insertion, indels	Missplicing, truncated protein	Reduced kinase activity	RP38	Jespersgaard *et al.*, 2020[189]; Rashid *et al.*, 2020[258]
Mevalonate kinase (MVK/251170)	Substitutions		Decreased activity	Mevalonic aciduria; hyper-IgD syndrome	Siemiatkowska *et al.*, 2013[190]
NIMA related kinase 2 (NEK2/604047)	Frameshift, missense	Nonsense-mediated decay of mRNA, truncated protein	Lack of kinase activity and loss of microtubule binding	RP67	Nishiguchi *et al.*, 2013[191]
Neuronal differentiation 1 (NEUROD1/601724)	Missense, frameshift		Partial loss of function	Maturity-onset diabetes of the young ; Type 2 diabetes mellitus	Wang *et al.*, 2014[192]
Nuclear receptor subfamily 2 group E member 3 (NR2E3/604485)	Missense, nonsense, insertion, splicing variants	Truncated protein	Mislocalization, decrease in DNA-binding, CRX-binding and homodimerization	RP37; enhanced S-cone syndrome; Goldmann–Favre syndrome; combined dominant and recessive retinopathy	Diakatou *et al.*, 2021[72]; Al-Khuzaei *et al.*, 2020[71]
Neural retina leucine zipper (NRL/162080)	Missense, frameshift	Truncated protein	Mislocalization, reduced transcriptional activity	RP27; retinal degeneration, clumped pigment type	Kanda *et al.*, 2007[102]
OFD1 centriole and centriolar satellite protein (OFD1/300170)	Missense, frameshift	Truncated protein		RP23; X-linked Joubert syndrome; orofaciodigital syndrome 1, Simpson-Golabi-Behmel syndrome 2	Chen *et al.*, 2018[169]; Webb *et al.*, 2012[234]
Phosphodiesterase 6A (PDE6A/180071)	Missense, nonsense, insertion, deletion, splice-site variants	Misfolding	Altered size, charge and hydrophobicity	RP43	Khan *et al.*, 2021[130]
Phosphodiesterase 6B (PDE6B/180072)	Missense, nonsense, insertion, deletion, indels, splice-site variants	Nonsense-mediated decay of mRNA, truncated protein	Loss of enzymatic activity	RP40; congenital stationary night blindness	Kuehlewein *et al.*, 2021[127]
Phosphodiesterase 6G (PDE6G/180073)	Splice-site variant	Incorrect splicing		RP57	Dvir *et al.*, 2010[194]
Protein O-linked mannose N-acetylglucosaminyltransferase 1 (beta 1,2-)	Missense, stop-gain	Abolishment of catalytic domain	Reduction in enzyme activity	RP76; muscular dystrophy-dystroglycanopathy, type	Xu *et al.*, 2016[195]

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Table 3: Contd...

Gene (Symbol/OMIM)	Mutation type	Protein change		Disease phenotypes	References
		Structural	Functional		
(POMGNT1/606822)				A, 3; muscular dystrophy-dystroglycanopathy, type B, 3; muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 3	
Photoreceptor disc component (PRCD/610598)	Missense, nonsense	Reduced expression, truncated protein	Mislocalization, non-functional protein	RP36	Spencer and Arshavsky 2019[259]; Pach *et al*., 2013[260]
Pre-mRNA processing factor 3 (PRPF3/607301)	Missense		Reduction in the phosphorylation of protein and suppression of protein-protein interactions	RP18	Yang *et al*., 2021[76]
Pre-mRNA processing factor 4 (PRPF4/607795)	Missense, deletion		Disruption of binding with PRPF3, loss of function	RP70	Linder *et al*., 2014[103]; Chen *et al*., 2014[261]
Pre-mRNA processing factor 6 (PRPF6/613979)	Missense		Mislocalization	RP60	Růžičková and Staněk 2017[67]
Pre-mRNA processing factor 8 (PRPF8/607300)	Missense, nonsense, frameshift, splice-site variants	Truncated protein, misfolding	Reduced activity and impaired interaction with SNRNP200	RP13	Escher *et al*., 2018[70]; Van Cauwenbergh *et al*., 2017[54]
Pre-mRNA processing factor 31 (PRPF31/606419)	Missense, nonsense, frameshift, indels, splice-site variants	Truncated protein	Reduced solubility and mislocalization	RP11	Wheway *et al*., 2020[33]
Peripherin 2 (PRPH2/179605)	Missense, nonsense, insertion, deletion, splicing variants	Altered confirmation, disruption of α-helical structure	Mislocalization,	RP7; macular dystrophy; digenic RP with ROM1; adult vitelliform macular dystrophy; cone-rod dystrophy; central areolar choroidal dystrophy; recessive LCA	Oishi *et al*., 2021[262]; Strafella *et al*., 2019[263]
Prominin 1 (PROM1/604365)	Missense, deletion	Non-sense mediated decay of mRNA, truncated protein	Loss of function, mislocalization or aberrant role in protein-trafficking	RP47; Stargardt-like macular dystrophy; macular dystrophy, bull's-eye; cone-rod dystrophy	Wang *et al*., 2021[199]; Permanyer *et al*., 2010[264]
Protein S (PROS1/176880)	Substitution	Altered confirmation		Thrombophilia due to protein S deficiency	Bushehri *et al*., 2019[200]
Retinol binding protein 3 (RBP3/180290)	Missense,	Misfolding, nonsense-mediated decay of mRNA	Loss of function	RP66	Arno *et al*., 2015[201]
Retinol dehydrogenase 12 (RDH12/608830)	Missense, nonsense, insertion, deletion	Truncated protein		RP53; Leber congenital amaurosis with severe childhood retinal dystrophy	Sarkar *et al*., 2020[105]
Receptor accessory protein 6 (REEP6/609346)	Deletion, missense	Nonsense-mediated decay, truncated protein	Protein instability, mislocalization	RP77	Zhang *et al*., 2021[265]; Lin *et al*., 2020[266]

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Table 3: Contd...

Gene (Symbol/OMIM)	Mutation type	Protein change		Disease phenotypes	References
		Structural	Functional		
Retinal G protein coupled receptor (RGR/600342)	Missense, frameshift, deletion, duplication	Truncated protein		RP44; choroidal sclerosis	Li *et al.*, 2016[205]
Rhodopsin (RHO/180380)	Missense, nonsense, deletions, insertions, splice-site variants	Altered folding and post-translational modifications	Mislocalization, impaired dimerization	RP4; congenital stationary night blindness; retinitis punctata albescens	Roman-Sanchez *et al.*, 2016[267]; Dias *et al.*, 2018[19]
Retinaldehyde binding protein 1 (RLBP1/180090)	Missense, deletion, frameshift	Truncated protein		Bothnia dystrophy; retinitis punctata albescens; Newfoundland rod-cone dystrophy; fundus albipunctatus	Al-Bdour *et al.*, 2020[268]
Retinal outer segment membrane protein 1 (ROM1/1807221)	Substitutions		Impaired oligomerization	RP7	Zulliger *et al.*, 2018[108]
RP1 axonemal microtubule associated (RP1/180100)	Missense, nonsense, frameshift, splicing variants	Nonsense-mediated mRNA decay, truncated protein		RP1	Georgiou *et al.*, 2021[60]; Wang *et al.*, 2021[55]
RP2 activator of ARL3 GTPase (RP2/312600)	Missense, nonsense, insertion, deletion, splice-site variants	Truncated protein, misfolding	Mislocalization, non-functional protein	RP2	Fujinami *et al.*, 2020[230]
RP1 like 1 (RP1L1/608581)	Missense, nonsense, frameshift		Loss of function	RP88; occult macular dystrophy	Noel *et al.*, 2020[209]
RP9 pre-mRNA splicing factor (RP9/180104)	Missense			RP9	Keen *et al.*, 2002[269]
retinoid isomerohydrolase RPE65 (RPE65/180069)	Missense, nonsense, splice-site variants		Altered isomerase function	RP20; Leber congenital amaurosis; Retinitis pigmentosa 87 with choroidal involvement	Lopez-Rodriguez *et al.*, 2021[270]; Li *et al.*, 2019[125]
Retinitis pigmentosa GTPase regulator (RPGR/310612)	Deletion, nonsense, frameshift, splice-site variants		Mislocalization	RP3; X-linked cone dystrophy 1; X-linked atrophic macular dystrophy, recessive	Vössing *et al.*, 2021[224]; Kortüm *et al.*, 2021[226]
S-antigen visual arrestin (SAG/181031)	Nonsense, frameshift	Truncated protein		RP47; Oguchi disease-1	Sonoyama *et al.*, 2011[271]
Sterile alpha motif domain containing 11 (SAMD11/616765)	Missense, nonsense, splice-site variant	Truncated protein			Corton *et al.*, 2016[210]
Semaphorin 4A (SEMA4A/607292)	Missense, frameshift		Mislocalization	RP35; cone-rod dystrophy 10	Schmidt-Kastner *et al.*, 2008[272]; Birtel *et al.*, 2018[273]
Solute carrier family 7 member 14 (SLC7A14/615720)	Missense		Mislocalization	RP68	Jin *et al.*, 2014[211]
Small nuclear ribonucleoprotein U5 subunit 200 (SNRNP200/601664)	Missense, splice-site variants			RP33	Gerth-Kahlert *et al.*, 2019[75]
Spermatogenesis associated 7 (SPATA7/609868)	Nonsense, missense,	Nonsense-mediated		Leber congenital amaurosis 3	Xiao *et al.*, 2019[214]

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Table 3: Contd...

Gene (Symbol/OMIM)	Mutation type	Protein change		Disease phenotypes	References
		Structural	Functional		
	frameshift, deletion, splice-site variants	decay of mRNA, truncated potein			
Secreted phosphoprotein 2 (SPP2/602637)	Missense		Mislocalization, impaired secretion		Liu *et al.*, 2015[113]
tRNA nucleotidyl transferase 1 (TRNT1/612907)	Insertion, splice variant	Truncated protein	Loss of function	Retinitis pigmentosa with erythrocytic microcytosis; Sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay	DeLuca *et al.*, 2016[214]
TOP1 binding arginine/serine rich protein, E3 ubiquitin ligase (TOPORS/609507)	Nonsense, insertion, deletion	Truncated protein	Adverse sumoylation of the protein, unstable protein	RP31	He *et al.*, 2022[274]; Selmer *et al.*, 2010[85]; Van Cauwenbergh *et al.*, 2017[54]
Tetratricopeptide repeat domain 8 (TTC8/608132)	Splice-site variant	Missplicing, premature termination of reading frame		RP51; Bardet–Biedl syndrome	Murphy *et al.*, 2015[275]
TUB like protein 1 (TULP1/602280)	Missense, splice-site, nonsense, frameshift, insertion	Misfolding, reduced protein-stability, missplicing		RP14; Leber congenital amaurosis 15	Woodard *et al.*, 2021[217]; Abbasi *et al.*, 2008[276]
Usherin (USH2A/276901)	Missense, nonsense, insertion, deletion, duplication, splice-site variants, pseudo-exon inclusion variants	Nonsense-mediated decay, truncated protein		RP39; usher syndrome, type 2a	Toualbi *et al.*, 2020[117]
Zinc finger protein 408 (ZNF408/616454)	Missense, frameshift, splice-site variants	Truncated protein	Loss of function	RP72; familial exudative vitreoretinopathy	Nadelmann *et al.*, 2021[277]
Zinc finger protein 513 (ZNF513/613598)	Missense	Failure of transcription		RP58	Li *et al.*, 2010[220]

regulator of retinal development. The RP-causing variants were identified in Pakistani families.[220,221]

X-linked retinitis pigmentosa

X-linked retinitis pigmentosa (XLRP) is the most drastic type of RP, having a very fast development of symptoms (legal blindness is attained in the third or fourth decade).[222] XLRP accounts for 10%–15% of all RP cases, with an occurrence of 1: 25,000 people. There is early onset of RP symptoms (first decade of life).[38] Six genes have been mapped for XLRP, of which only three genes are identified and the other three are unidentified. The identified genes include *RPGR*, *RP2* and *OFD1*. *RPGR* and *RP2* are the major genes covering 85%–95% of XLRP cases.[223]

GTPase regulator gene for retinitis pigmentosa

GTPase regulator gene for retinitis pigmentosa (*RPGR*) was the first identified gene (in 1996) for XLRP. It is located at the position Xp11.4.[223] *RPGR* is associated with 80% of XLRP cases, 10%–20% of cases of familial RP, and 12%–15% of all the sporadic cases. It is made up of 22 exons that encode for the RPGR protein.[224,225] This protein is involved in microtubule organization and ciliary protein trafficking.[226]

Of these, 10 different isoforms of RPGR protein are known, of which only two are the major isoforms: $RPGR^{ex1\text{-}19}$ and $RPGR^{ORF15}$.[223] The N-terminus of both isoforms encodes for a regulator of a chromosome condensation 1-like domain or RCC1-like domain (RLD). The $RPGR^{ex1\text{-}19}$ isoform, also called the constitutive isoform, includes all the exons from 1 to 19. It encodes a protein of 815 amino acids expressed throughout the body. It shows expression in the axoneme of the primary cilia. The $RPGR^{ORF15}$ isoform is retina-specific and is expressed in photoreceptor connecting cilia.[224] It encodes for a protein of 1152 amino acids. The terminal exon of this isoform contains

a purine-rich sequence. The repetitive nature of this sequence makes it prone to variations.[83] Most of the ORF15 variants show premature truncation of the protein.[225] The constitutive isoform plays an important role in early eye development, whereas the retina-specific isoform plays a role in the mature retina.[227] In mouse models, it has been shown that fine tuning of these two major isoforms is vital for proper functioning of the RPGR protein.[225]

More than 500 genetic variants of *RPGR* are known to be involved in various retinal dystrophies, most of which are frameshift and nonsense, while 10% of the variants are splice site variants.[226] Variants of *RPGR* affect protein trafficking and, thus, also have an adverse effect on the function and survival of photoreceptors.[228]

Retinitis pigmentosa2 gene

The second gene identified for XLRP is **retinitis pigmentosa2 *(RP2)***.[229] It was identified in 1998 by linkage analysis.[230] It is located at position Xp11.3 and spans 1 kb of the DNA. It consists of five exons which encode a protein of 350 amino acids.[229] Protein is expressed in the plasma membrane of the photoreceptors, RPE, and also in many other cells of the retina.[230] It has two domains: the tubulin folding cofactor C-like domain (TBCC domain) towards the N-terminus and the nucleoside diphosphate kinase-like domain (NDPK) towards the C-terminus.[231] In the photoreceptor cells, it shows GTPase-activating function for Arf-like 3 (Arl3, a small G-protein) and binds to it through its N-terminal region. Assembly of these two proteins at the connecting cilium plays a vital role in trafficking of the membrane proteins (GRK1, PDE6 and transducin) and cilia proteins, including phosphodiesterases, nephrocystin 3 and kinesin motor proteins, to the outer segment of the photoreceptor cells. This has been proven by mouse models.[229,232]

Severe symptoms, early age of disease onset, fast progression rate, and early macular degeneration have been observed in cases of RP2 disease.[229,233] Males are more severely affected in comparison to females and become legally blind in the fourth decade of their lives.[233]

Ubiquitous expression of the protein is unable to explain why the variants have adverse effects only on photoreceptor cells. This may be due to high metabolic activity of the photoreceptor cells for which they require uninterrupted protein trafficking from IS to OS.[231] In this gene, 133 variations are known to cause the disease. Of them, 43 variations are missense, 15 are splice site variations, 14 are nonsense variations and 50 are insertion/deletion or other types of variations.[230] The TBCC domain is known as the variational hotspot. Most of the variations have been described in the 2nd exon.[231] More than 50% of *RP2* variants result in the disease by destabilization and finally degradation of the protein.[232]

OFD1 centriole and centriolar satellite protein (*OFD1*) gene is located at Xp22.2 with 27 exons. The gene encodes for a protein involved in regulation of ciliogenesis and neuroprotection. It is involved in the pathogenesis of Joubert syndrome, orofaciodigital syndrome and RP23.[169,234]

The involvement of various genes in the pathogenesis of non-syndromic retinitis pigmentosa are summarized in Table 3.

Conclusion

Retinitis pigmentosa is the most common inherited retinal dystrophy causing irreversible blindness. It is characterized by continuous retinal degeneration which eventually leads to irreversible loss of vision. So far, there has been no universal cure for RP; only the blind people can be managed or the degeneration rate of the photoreceptors can be slowed down. Thus, development of treatments to prevent the disease is necessary. In this review, we have discussed the heterogeneity of this disease in terms of genetics. To make treatment possible, understanding the genetic heterogeneity of the disease is the most important thing. So that each phenotype related to various genetic variations could be treated.

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Conflicts of interest

There are no conflicts of interest.

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