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

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. It is one of the leading causes of bilateral and irreversible blindness in adults. 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. 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.). In another study, the prevalence was seen at approximately 1 in 930 in urban areas, and 1 in 372 in rural areas. In the case of central India, the occurrence of RP is 1:750 in adults aged 30+ years of the rural population. Its high prevalence makes it the most common form of IRD.

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 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). 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. 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. 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.

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

RP is an inheritable group of disorders and follows various patterns of inheritance. It is a very complex disease genetically. There are inter- or intra-familial variations related to development, penetrance, and expressivity of the disease. 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).

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.

Clinical, genetic and morphological heterogeneity of RP makes it an extremely complicated ocular impairment. It is so complicated that it is known as a “fever of unknown origin”. 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 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. 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.

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. This also increases the complexity of the genetics of the RP disease. 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. 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. 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).

### Autosomal dominant RP

Autosomal dominant RP (ADRP) covers almost 30%–40% of all RP patients, 38% of which include gene defects disturbing splicing patterns. Uncontrolled splicing may result in various human diseases, but most of such variations are related to ADRP (with unknown reason). More than 20 distinct genes have been shown to cause ADRP, while only some of these cover a pertinent percentage of patients. 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. 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. It is the most studied G-protein-coupled receptor (GPCR). The characteristic three-dimensional structure of rhodopsin consists of seven
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.\(^{[23]}\) 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.\(^{[27]}\) In the rhodopsin gene, 150 variations have been identified for RP phenotypes.\(^{[28]}\) These variations are spread out over the entire length of the gene.\(^{[29]}\) The amino acid positions 135, 190, and 347 are the hot spots for variations in the worldwide population of RP.\(^{[30]}\) Variations in the cytoplasmic domain of the gene result in a more severe form of the symptoms in comparison to the intradiscal domain.\(^{[31,32]}\) The variation pro347leu in the RHO gene results in the most severe form of RP.\(^{[33]}\) 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.\(^{[34]}\)

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.\(^{[35,36]}\)

### 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.\(^{[37]}\)

The most common splicing factor gene for ADRP is PRPF31.\(^{[38]}\) Splicing factors are essential for retinal development and maintaining visual function.\(^{[39]}\) 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.\(^{[40]}\) 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.\(^{[41]}\)

In PRPF31, a huge number of genetic variations (>100) have been identified which cover 5%–10% of ADRP cases.\(^{[42]}\) 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.\(^{[43]}\) 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.\(^{[44]}\) Patients have been shown to reach complete blindness up to the age of 30.\(^{[45]}\)

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.\(^{[46,47]}\)

### Peripherin2 gene

The Peripherin2 (PRPH2) 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.\(^{[48]}\) Abnormalities in the PRPH2 gene were initially observed to cause retinal degeneration in rats, and hence named as retinal degeneration slow.\(^{[49]}\) Variations in this PRPH2 gene were observed in the pathogenesis of ADRP in 1991 for the first time.\(^{[50]}\) It is one of the most frequent causes of ADRP.\(^{[51]}\) Five to nine percent of all ADRP patients are covered by gene defects in PRPH2. Digenic RP can also be seen here when there are variations in both genes (PRPH2 and ROM1). The human PRPH2/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.\(^{[52]}\)
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.\(^\left[45\right]\) It acts as oligomers (composed of dimers) which form tetramers, mediated by the D2 loop.\(^\left[46\right]\) 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.\(^\left[48\right]\) 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.\(^\left[45\right]\)

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.\(^\left[48\right]\) More than 175 variations in the PRPH 2 gene are known to cause various retinal dystrophies.\(^\left[49\right]\) Genetic variations in this gene are also related to other retinal dystrophies.\(^\left[50\right]\) The frequency of PRPH2 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.\(^\left[51–54\right]\)

Retinitis pigmentosa1 gene

The retinitis pigmentosa1 gene (RP1) is made up of four exons, but only the last three exons are protein-coding.\(^\left[50\right]\) Exon number 4 is the largest one and forms 85% of the coding region of the protein.\(^\left[54\right]\) In 1999, the gene was observed to be involved in ADRP for the first time.\(^\left[55\right]\) It was the fourth gene to be identified for ADRP.\(^\left[56\right]\) It accounts for 5.5% of ADRP cases and 1% of autosomal recessive RP (ARRP) cases.\(^\left[57\right]\)

The gene encodes a protein of 2156 amino acids (240 kDa), which is a photoreceptor-specific microtubule-associated protein.\(^\left[59\right]\) Initially, the protein was named oxygen-regulated protein-1. But now, it is known as retinitis pigmentosa1 due to its involvement in ADRP.\(^\left[56\right]\) 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.\(^\left[59\right]\) For survival of the photoreceptors, the DCX domain is very essential.\(^\left[56\right]\) 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 ciliary structure and outer segment disc membranes’ stabilization.\(^\left[59\right]\)

RP1 is related to both ADRP (mostly) and ARRP (rarely).\(^\left[59,60\right]\) 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.\(^\left[61\right]\)

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.\(^\left[55\right]\) Amino acid residues between 500 and 1053 (in exon 4) act as a variational hotspot for ADRP.\(^\left[62\right]\)

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 RPI, 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.\(^\left[63\right]\) 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.\(^\left[54\right]\)

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.\(^\left[54,64\right]\) It is located at the position 7q32.1 with 18 exons. Genetic variants are associated with ADRP (mostly) and leber congenital amaurosis (LCA, rarely).\(^\left[65\right]\) 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.\(^\left[60\right]\)

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.\(^\left[66\right]\)

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.\(^\left[66\right]\) 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.\(^\left[66\right]\)

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.\(^\left[67\right]\) 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. 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.

In spite of ubiquitous expression, variations exclusively result in retinal dysfunctioning. PRPF8-mediated RP is a result of ciliary dysfunctioning. Twenty-two variations have been identified in PRPF8 for RP13, most of which are confined to the terminal exon (Jab1/MPN domain). 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.

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).

**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 pigmented retinal degeneration.

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. 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.

After P23H in RHO, G56R in NR2E3 is the second most common variation causing ADRP. 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.

**Small nuclear ribonucleoprotein U5 subunit 200 (snRNP200) gene**

Small nuclear ribonucleoprotein U5 subunit 200 (snRNP200) gene is located at 1q11.2 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 hBr2, having 2136 amino acid residues) which catalyzes the unwinding (ATP-dependent) of U4/U6 which is crucial for spliceosome activation. 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. Variational hotspots for RP are associated with the U4 snRNP binding channel. 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.

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. Variant frequency of snRNP200 for ADRP is 5.8%, 2.3% and 1.5% in Chinese, Spanish and American cohorts, respectively.

**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. The gene accounts for 1%–2% of ADRP cases.

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. It is a protein of BTB-Kelch family playing a role in ubiquitylation. 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. Biological function of this protein has not been very clear yet. In the retina, it is thought to stabilize the E3 ligase complex formation. 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.

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.

**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). The protein structure has three domains: homeodomain (binds with the DNA of other retinal genes), Wisp 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. 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.

**Pre-mRNA processing factor 3 gene**

The pre-mRNA processing factor 3 (PRPF3) gene is located at position 14q21.2 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: PWW, PRF3 and DUF1115. 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).[56]

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.[56] It has been identified in various ADRP populations, including American, Danish, English, Japanese, Korean, Spanish, and Swiss.[83]

**TOPORS**

**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 1.[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 cilium 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%–2% 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 RIP2 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.[80,89]

**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 vitreoretinoidopathy, 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 guanylate cyclase activator 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, rhesus 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 IFM 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.[108]

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 ARRPP. Gain-of-function variants result in ADRP (early onset, RP27), while the loss-of-function variants are known to cause ARRPP.[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 retinal 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 11q23.3 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 cysteine 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.[88] 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). 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 ARRPP 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.[118] More than 1100 pathogenic variants of USH2A gene are known, including missense, nonsense, splicing, deletions, insertions, indels, and large rearrangement.[119] 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, ARRPP (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; AAl038Val] 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 333 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.\[128\] 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.\[128\]

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 complex gene

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.\[126\] 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 achronatopia. Of all the cases of ARRP, 8% resulted from variations in the rod-specific PDE6 gene family.\[126\] 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, photosensitized 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.\[128\]

### 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).\[126\] 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).\[139,140\] It has relatively high prevalence in Asian populations (7.6% in Chinese population and 8.1% 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. 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.

In case of RP25 gene, truncating variations are the most common disease-causing variations. 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. A large number of disease-causing variations are found close to the C-terminal region of the protein. 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.

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 Müller 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.

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. 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.

CRB1-associated diseases include RP12, LCA, and maculopathy. It is responsible for 17% of LCA cases in Spain. 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. Most of the variations are found in exons 9 (41%) and 7 (27%).

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. It has a complex expression due to alternative splicing (>20 transcripts expressing in various tissues). 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). 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.

The protein shows 29% similarity with ceramide kinase. But, kinase activity is not reported for it. 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.

It is known to cause ARRP (RP26) and also CORD. 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. In CERKL, 39 variants have been identified for IRDs and p.Arg257Stop is the most prevalent variant of CERKL. Variants result in increased oxidative stress and eventually lead to retinal degeneration.

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).

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.Cys147Tyr is responsible for 36% of ADRP cases in the Hispanic cohort.

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 ADRP.

The AGBL carboxypeptidase 5 (AGBL5) gene is located at 2p3.3 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.

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.

The Rho/Rac guanine nucleotide exchange factor 18 (ARHGDEF18) 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.

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.

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 ARR[3,166]

The Bardet–Biedl syndrome 1 (BB1) gene is located at 11q13.2 with 17 exons. The encoded protein plays a role in eye development. Genetic variants are known to cause ARR and Bardet–Biedl syndrome.[167]

The Bardet–Biedl syndrome 2 (BB2) 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. The encoded protein is 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 ARR, 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 1b, 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 ARR and have been identified in patients from Saudi Arabia.[178]

The endosulfine alpha (ENSA) gene is located at 1q21.3 with six exons. It encodes for an endogenous ligand for sulfonlurea receptor 1 which regulates KATP channels. Genetic variants are known to cause RP.[179]

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.[180]

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.[181]

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.[182]

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.[183]

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.[184]

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 matrix (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.[185]

The KIAA1549 gene is located at 7q34 with 21 exons. The encoded protein may be involved in retina-specific function. Genetic variants are known to cause RP86.[186]

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.[187]

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.[188]

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.[189]
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.\cite{206}

The mevalonate kinase (MVK) gene is located at 12q24.11 with 13 exons. Genetic variants are associated with the phenotypes including Hyper-1qD syndrome, Mevalonic aciduria, Porokeratosis 3, multiple types and RP.\cite{207}

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.\cite{208}

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.\cite{209}

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.\cite{210}

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.\cite{211}

The accession number 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.\cite{212}

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.\cite{213,214}

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.\cite{215,216}

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.\cite{217}

The retinal 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.\cite{218,219}

The receptor accessory protein 6 (REEP6) gene is located at 1p13.3 with six exons. The encoded protein regulates the structure of ER and is involved in the pathogenesis of RP77.\cite{220}

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.\cite{221,222}

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.\cite{223,224}

The RP1 like 1 (RPL1) 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.\cite{225,226}

The soluble 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.\cite{227}

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.\cite{228,229}

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.\cite{230}

The tetraticopeptide 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.\cite{231}

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.\cite{232,233}

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.\cite{234,235}

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/](https://sph.uth.edu/retnet/))

| Gene (Symbol/OMIM) | Chromosomal Location | Inheritance pattern | Protein Function | 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 | CO₂ 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 (CLRN1/604210) | 3q25.1 | AR | Clarin-1 | Role in hair cell and photoreceptor synapses |
| Cyclic nucleotide gated channel subunit alpha 1 (CNGB1/123825) | 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 (CRIX/602225) | 19q13.33 | AD | Cone-rod otx-like photoreceptor homeobox transcription factor | Differentiation and maintenance of photoreceptor cells |

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 Recovery of phototransduction                     |
| Guanylate cyclase activator 1B (GUCA1B/602275)          | 6p21.1               | AD                  | guanylate cyclase activating protein 1B                                            |
| 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-ketoglutarate 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 (IMP1/602870)   | 6q14.1               | AD, AR              | Interphotoreceptor matrix proteoglycan 1 Component of the photoreceptor extracellular matrix |
| Interphotoreceptor matrix proteoglycan 2 (IMP2/607056)   | 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 |

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/604683) | 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 regulates 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 leucine 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/180571) | 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-) (POMGNT1/604682) | 1q34.1 | 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-snmp 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-snmp 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-snmp |
| 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 |

Contd...
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                          |
| Retinol binding protein 3 (RBP3/180290)                 | 10q11.22             | AR                  | Retinol binding protein 3, interstitial                |
| Retinol dehydrogenase 12 (RDH12/608830)                | 14q24.1              | AD, AR              | Retinol dehydrogenase 12                               |
| Receptor accessory protein 6 (REEP6/609346)             | 19p13.3              | AR                  | Receptor accessory protein 6 (receptor expression enhancer protein 6) |
| Retinal G protein coupled receptor (RGR/600342)         | 10q23.1              | AD, AR              | RPE-retinal G protein-coupled receptor                 |
| Rhodopsin (RHO/180380)                                 | 3q22.1               | AD, AR              | Rhodopsin                                             |
| Retinaldehyde-binding protein 1 (RLBP1/180090)          | 15q26.1              | AD                   | 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                                           |
| RP2 activator of ARL3 GTPase (RP2/312600)              | Xp11.23              | XL                  | Retinitis pigmentosa 2 (X-linked)                      |
| RP1 like 1 (RP1L1/608581)                              | 8p23.1               | AD, AR              | Retinitis pigmentosa 1-like protein 1                  |
| RP9 pre-mRNA splicing factor (RP9/180104)              | 7p14.3               | AD                   | RP9 protein or PIM1-kinase associated protein 1        |
| Retinoid isomerohydrolase RPE65 (RPE65/180069)        | 1p31.2               | AD, AR              | Retinal pigment epithelium-specific 65 kD protein      |
| Retinitis pigmentosa GTPase regulator (RPGR/310612)   | Xp11.4               | XL                  | Retinitis pigmentosa GTPase regulator                  |
| 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       |
| Semaphorin 4A (SEMA4A/607292)                          | 1q22                 | AD, AR              | Semaphorin 4A                                         |
| Solute carrier family 7 member 14 (SLC7A14/615720)     | 3q26.2               | AR                  | Solute carrier family 7 member 14                      |
| Small nuclear ribonucleoprotein US 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              |
| TOP1 binding arginine/serine                           | 9p21.1               | AD                  | tRNA function and protein synthesis                   |

Contd...
### Table 3: Contd...

| Gene (Symbol/OMIM) | Chromosomal Location | Inheritance pattern | Protein Function | Chromosomal Location | Inheritance pattern | Protein Function |
|--------------------|----------------------|---------------------|------------------|----------------------|---------------------|------------------|
| rich protein, E3 ubiquitin ligase (TOPORS/609507) | 14q32.11 | AR | tetrmericopeptide repeat domain 8 | 6p21.31 | AR | Tubby-like protein 1 |
| Tetramericopeptide repeat domain 8 (TTC8/608132) | 6p21.31 | AR | Tubby-like protein 1 | 14q32.11 | AR | Basal body - ciliary function |
| Usherin (USH2A/276901) | 1q41 | AR | Tctetramericopeptide repeat domain 8 | 11p11.2 | AD, AR | Zinc finger protein 408 |
| Zinc finger protein 408 (ZNF408/616454) | 11p11.2 | AD, AR | Zinc finger protein 513 | 14p23.3 | AR | Zinc finger protein 513 |
| Zinc finger protein 513 (ZNF513/613598) | 14p23.3 | AR | Zinc finger protein 513 | 2p23.3 | AR | Zinc finger protein 513 |
| 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[87] |
| Aryl hydrocarbon receptor (AHR/600253) | Splice-site variant | Truncated protein | Loss of transcriptional activity | RP85 | Zhou et al., 2018[122] |
| Rho/Rac guanine nucleotide exchange factor 18 (ARHGEF18/616432) | Deletion, missense, nonsense | Truncated protein | RP78 | Arno et al., 2017[123] |
| 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 BBosome | RP55; Bardet–Biedl syndrome | Singh et al., 2020[236]; Chandrasekar et al., 2018[195]; Pretorius et al., 2014[237] |
| ADP ribosylation factor like GTPase 2 binding protein (ARL2BP) | Missense, splice-site variants | Abnormal splicing | Reduced binding to ARL2, mislocalization | RP5; Bardet–Biedl syndrome | Fadaie et al., 2016[196]; Xu et al., 2015[238] |
| Bardet–Biedl syndrome 1 (BBS1/209900) | Missense | Splicing defect | RP74; Bardet–Biedl syndrome | RP50; macular dystrophy, best type; vitreoretinohoroidopathy; bestrophinopathy | Hartzell et al., 2008[239] |
| Bardet–Biedl syndrome 2 (BBS2/606151) | Missense, nonsense | Ca++ signaling | RP54 | Nishimura et al., 2010[240] |
| Bestrophin 1 (BEST1/607854) | Missense, nonsense, frameshift | Reduced protein stability | RP54 | Nishimura et al., 2010[240] |
| Chromosome 2 open reading frame 71 (C2orf71/613425) | Nonsense, missense | Reduced protein stability | RP54 | Nishimura et al., 2010[240] |

Contd...
Table 3: Contd...

| Gene (Symbol/OMIM)                                      | Mutation type          | Protein change | Disease phenotypes                                                   | References                                                                 |
|---------------------------------------------------------|------------------------|----------------|-----------------------------------------------------------------------|---------------------------------------------------------------------------|
| 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[21]; Chen et al., 2018[22]                   |
| Carbonic anhydrase 4 (CA4/114760)                        | Substitutions          | Misfolding     | Mislocalization                                                      | RP17                                                                      | Tian et al., 2010[23]; Datta, R., 2010[24]                                   |
| Ceramide kinase like (CERKL/608381)                      | Nonsense, missense, splicing, frameshift | Truncated protein | RP26; cone-rod dystrophy with inner retinopathy                     | Nadeem et al., 2020[25]; Downes et al., 2020[26]                         |
| Chloride channel CLIC like 1 (CLCC1/617539)              | Missense               | Misfolding     | Decreased channel activity                                           | RP32                                                                      | Li et al., 2018[177]                                                        |
| Clarin 1 (CLRN1/606397)                                  | Missense               | Truncated protein, | RP61; usher syndrome                                                 | Isosomppi et al., 2009[27]                                                 |
| Cyclic nucleotide gated channel subunit alpha 1 (CNGA1/123825) | Missense, nonsense, deletion, splice-site variants | Nonfunctional protein |                                                         |                                                                            | Wang et al., 2016[28]; Saito et al., 2021[29]                                 |
| Cyclic nucleotide gated channel subunit beta 1 (CNGB1/600724) | Missense, nonsense, splicing, insertion, deletion, duplication, indels | Truncated protein, | RP45                                                                  | Nissisi et al., 2021[30]                                                   |
| Crumbs cell polarity complex component 1 (CRB1/604210)   | Missense, nonsense, insertion, deletion, splice variants | Altered hydrophobicity and chargeability, impaired protein-protein interaction and calcium-binding activity | RP12; retinitis pigmentosa with paraarteriolar preservation of the RPE; leber congenital amaurosis; pigmented paravenous chorioretinal atrophy | Mairot et al., 2021[31]; Guo et al., 2019[32]; Lu et al., 2016[33]; Beryozkin et al., 2013[34] |
| Cone-rod homeobox (CRX/602225)                           | Missense, nonsense, deletion, insertion, indels | Truncated protein | Impaired DNA-binding and loss of transactivation activity             | Cone-rod dystrophy; recessive, and de novo Leber congenital amaurosis     | Tran and Chen 2014[35]                                                      |
| CWC27 spliceosome associated cyclophilin (CWC27/617170)   | Frameshift             | Truncated protein | Retinitis pigmentosa and skeletal anomalies                           |                                                                           | Xu et al., 2017[36]                                                        |
| Cytochrome P450 family 4 subfamily V member 2 (CYP4V2/608614) | Splice-site variant | Impaired splicing | Bietti crystalline corneoretinal dystrophy                           |                                                                           | Wang et al., 2012[37]                                                      |
| Dehydrodolichyl diphosphate synthase subunit (DHDDS/608172) | Missense               | Altered splicing activity | RP59; congenital disorder of glycosylation, type 1bb; developmental delay and seizures with or without movement abnormalities |                                                                           | Brandwine et al., 2021[38]                                                 |
| DEAH-box helicase 38 (DHX38/605584)                       | Missense               | Misfolding     | RP84; macular coloboma                                                |                                                                           | Latif et al., 2018[39]                                                     |
| ER membrane protein complex subunit 1 (EMC1/616846)       | Missense, splicing variants | Truncated protein |                                                                           |                                                                           | Cabet et al., 2020[40]                                                     |
| Endosulfine alpha (ENSA/603061)                           | Deletion               | Truncated protein |                                                                           |                                                                           | Yi et al., 2020[41]                                                       |

Contd...
| Gene (Symbol/OMIM) | Mutation type | Protein change | Disease phenotypes | References |
|-------------------|---------------|----------------|---------------------|------------|
| 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[200] |
| 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 | RP48; macular dystrophy | Avesani et al., 2021[250] |
| Guanylate cyclase activator 1B (GUCA1B/608275) | Missense | Misslocalization | Lack of enzymatic activity | Martins et al., 2019[255]; Haer-Wigman et al., 2015[182] |
| Heparan-alpha-glucosaminide N-acetyltransferase (HGSNAT/610453) | Missense, nonsense, deletion, insertion, frameshift, splice-site variant | Nonsense-mediated decay of mRNA, misfolding, truncated protein | | |
| Gene (Symbol/OMIM) | Mutation type | Protein change | Disease phenotypes | References |
|--------------------|---------------|----------------|-------------------|------------|
| Lecithin retinol acyltransferase (LRAT/604863) | Deletion | Nonsense-mediated decay of mRNA, truncated protein | Leber congenital amaurosis | Koster et al., 2021[187] |
| Male germ cell associated kinase (MAK/154235) | Alu insertion, missense | Truncated protein | RP62 | Cho et al., 2020[256]; Ozgül et al., 2011[257] |
| MER proto-oncogene, tyrosine kinase (MERTK/604705) | Missense, nonsense, splice-site variants, deletion, insertion, indels | Missplicing, truncated protein | RP38 | Jespersgaard et al., 2020[189]; Rashid et al., 2020[258] |
| Mevalonate kinase (MVK/251170) | Substitutions | Decayed mRNA, truncated protein | 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 | Loss of kinase activity and loss of microtubule binding | 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 | RP37; enhanced S-cone syndrome; Goldmann-Favre syndrome; combined dominant and recessive retinopathy | Diakatou et al., 2021[102]; Al-Khuzaei et al., 2020[71] |
| Neural retina leucine zipper (NRL/162080) | Missense, frameshift | Truncated protein | Mislocalization, reduced transcriptional activity | Kanda et al., 2007[102] |
| OFD1 centriole and centriolar satellite protein (OFD1/300170) | Missense, frameshift | Truncated protein | RP23; X-linked Joubert syndrome; orofaciiodigital syndrome 1, Simpson-Golabi-Behmel syndrome 2 | Chen et al., 2018[193]; Webb et al., 2012[254] |
| Phosphodiesterase 6A (PDE6A/180071) | Missense, nonsense, insertion, deletion, splice-site variants | Misfolding | Altered size, charge and hydrophobicity | 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 | Kuehlewein et al., 2021[127] |
| Phosphodiesterase 6G (PDE6G/180073) | Splice-site variant | Incorrect splicing | RP40; congenital stationary night blindness | Khan et al., 2021[130] |
| Protein O-linked mannose N-acetylglucosaminyltransferase 1 (beta 1,2-) | Missense, stop-gain | Abolishment of catalytic domain | Reduction in enzyme activity | Dvir et al., 2010[194]; Xu et al., 2016[195] |

Contd...
### Table 3: Contd...

| Gene (Symbol/OMIM)                                      | Mutation type                          | Protein change                        | Disease phenotypes                                                                 | References                                                                 |
|---------------------------------------------------------|----------------------------------------|---------------------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| (POMGNT1/606822)                                        |                                        |                                       | A, 3: muscular dystrophy-dystroglycanopathy, type B, 3: muscular dystrophy-dystroglycanopathy (limb-girdle), type C | Spencer and Arshavsky 2019\[^{259}\], Pach et al., 2013\[^{260}\] |
| Photoreceptor disc component (PRCD/610598)               | Missense, nonsense                      | Reduced expression, truncated protein  | Mislocalization, non-functional protein                                             | RP36                                                                       |
| 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                                                                                  | Ružičková and Staněk 2017\[^{267}\]                                       |
| Pre-mRNA processing factor 8 (PRPF8/607300)              | Missense, nonsense, frameshift, splice-site variants | Truncated protein                      | RP13                                                                                  | Escher et al., 2018\[^{268}\], Yan Cauwenbergh et al., 2017\[^{269}\]             |
| Pre-mRNA processing factor 31 (PRPF31/606419)            | Missense, nonsense, frameshift, indels, splice-site variants | Truncated protein                      | RP11                                                                                  | Wheway et al., 2020\[^{230}\] |
| Peripherin 2 (PRPH2/179605)                              | Missense, nonsense, insertion, deletion, splicing variants | Altered confirmation, disruption of α-helical structure | Mislocalization,                                      | Oishi et al., 2021\[^{262}\], Strafella et al., 2019\[^{233}\] |
| Prominin 1 (PROM1/604365)                               | Missense, deletion                      | Non-sense mediated decay of mRNA, truncated protein | Loss of function, mislocalization or aberrant role in protein-trafficking           | Wang et al., 2021\[^{263}\], Pernamyer et al., 2010\[^{234}\] |
| Protein S (PROS1/176880)                                | Substitution                            | Altered confirmation                   | Thrombophilia due to protein S deficiency                                             | Bushehri et al., 2019\[^{266}\]                                               |
| Retinol binding protein 3 (RBP3/180290)                  | Missense                                | Misfolding, nonsense-mediated decay of mRNA | Loss of function                                                      | Arno et al., 2015\[^{231}\]                                               |
| Retinol dehydrogenase 12 (RDH12/608830)                  | Missense, nonsense, insertion, deletion | Truncated protein                      | RP53; Leber congenital amaurosis with severe childhood retinal dystrophy             | Sarkar et al., 2020\[^{235}\]                                               |
| Retinol dehydrogenase 12 (RDH12/608830)                  | Deletion, missense                      | Nonsense-mediated decay, truncated protein | Protein instability, mislocalization                                                | Zhang et al., 2021\[^{264}\], Lin et al., 2020\[^{236}\] |

Contd...
**Table 3: Contd...**

| Gene (Symbol/OMIM) | Mutation type | Protein change | Disease phenotypes | References |
|--------------------|---------------|----------------|--------------------|------------|
| Retinal G protein coupled receptor (RGR/600342) | Missense, frameshift, deletion, duplication | Truncated protein | RP44; choroidal sclerosis | Li et al., 2016[206] |
| Rhodopsin (RHO/180380) | Missense, nonsense, deletions, insertions, splice-site variants | Altered folding and post-translational modifications | Mislocalization, impaired dimerization | Roman-Sanchez et al., 2016[207]; Dias et al., 2018[196] |
| 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 axonal 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, deletion, splice-site variants | Truncated protein, misfolding | Mislocalization, non-functional protein | Fujinami et al., 2020[230] |
| RP1 like 1 (RP1L1/608581) | Missense, nonsense, frameshift | Loss of function | RP88; occult macular dystrophy | Noel et al., 2020[290] |
| RP9 pre-mRNA splicing factor (RP9/180104) | Missense, frameshift | | RP9 | Keen et al., 2002[299] |
| 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[226]; Kortüm et al., 2021[226] |
| S-antigen visual arrestin (SAG/181031) | Nonsense, frameshift | Truncated protein | RP47; Oguchi disease-1 | Sonoyma et al., 2011[271]; Corton et al., 2016[210] |
| Sterile alpha motif domain containing 11 (SAMD11/616765) | Missense, nonsense, splice-site variant | Truncated protein | | |
| Semaphorin 4A (SEMA4A/607292) | Missense, frameshift | Mislocalization | RP35; cone-rod dystrophy 10 | Schmidt-Kastner et al., 2008[272]; Birtel et al., 2018[273]; Jin et al., 2014[215] |
| Solute carrier family 7 member 14 (SLC7A14/615720) | Missense | Mislocalization | RP68 | |
| Small nuclear ribonucleoprotein US subunit 200 (SNRNP200/601664) | Missense, splice-site variants | | RP33 | Gerth-Kahler et al., 2019[275] |
| Spermatogenesis associated 7 (SPATA7/609868) | Nonsense, missense, nonsense-mediated | | Leber congenital amaurosis 3 | Xiao et al., 2019[214] |

Contd...
Table 3: Contd...

| Gene (Symbol/OMIM) | Mutation type | Protein change | Disease phenotypes | References |
|--------------------|---------------|----------------|--------------------|------------|
|                    |               | Structural     | Functional         |            |
| Secreted phosphoprotein 2 (SPP2/602637) | Missense | Decay of mRNA, truncated protein | Mislocalization, impaired secretion | Liu et al., 2015[113] |
| tRNA nucleotidyl transferase 1 (TRNT1/612907) | Insertion, splice variant | Truncated protein | Loss of function | 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 | 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 | | |
| 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, 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 | 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: RPGRex1‑19 and RPGRex19. [223] The N-terminus of both isoforms encodes for a regulator of a chromosome condensation 1-like domain or RCC1-like domain (RLD). The RPGRex1‑19 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 RPGRex19 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. Most of the ORF15 variants show premature truncation of the protein. The constitutive isoform plays an important role in early eye development, whereas the retina-specific isoform plays a role in the mature retina. In mouse models, it has been shown that fine tuning of these two major isoforms is vital for proper functioning of the RPGR protein.

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. Variants of RPGR affect protein trafficking and, thus, also have an adverse effect on the function and survival of photoreceptors.

**Retinitis pigmentosa2 gene**

The second gene identified for XLRP is *retinitis pigmentosa2* (RP2). It was identified in 1998 by linkage analysis. 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. Protein is expressed in the plasma membrane of the photoreceptors, RPE, and also in many other cells of the retina. 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. In the photoreceptor cells, it shows GTPase-activating function for Arf-like 3 (Arf3, 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, nephrocytin 3 and kinesin motor proteins, to the outer segment of the photoreceptor cells. This has been proven by mouse models.

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

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. 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. The TBCC domain is known as the variational hotspot. Most of the variations have been described in the 2nd exon. More than 50% of RP2 variants result in the disease by destabilization and finally degradation of the protein.

**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 RP2.

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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