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Review Article

A review of recent developments in retinitis pigmentosa genetics, its clinical features, and natural course

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ABSTRACT

Background: Retinitis pigmentosa (RP), an inherited degenerative ocular disease, is considered the most common type of retinal dystrophy. Abnormalities of the photoreceptors, particularly the rods, and of the retinal pigment epithelium, characterizes this disease. The abnormalities progress from the midperiphery to the central retina. We here reviewed the developments in RP genetics in the last decade, along with its clinical features and natural course.
Methods: The present review focused on articles in English language published between January 2008 and February 2020, and deposited in PubMed/MEDLINE and Google Scholar databases. We searched for articles reporting on the clinical manifestations and genes related to both syndromic and non-syndromic RP. We screened and analyzed 139 articles, published in the last decade, referring to RP pathogenesis and identified, summarized, and highlighted the most significant genes implicated in either syndromic or non-syndromic RP pathogenesis, causing different clinical manifestations.
Results: Recent literature revealed that approximately 80 genes are implicated in non-syndromic RP, and 30 genes in syndromic forms, such as Usher syndrome and Bardet–Biedl syndrome (BBS). Moreover, it is estimated that 27 genes are implicated in autosomal dominant RP (adRP), 55 genes in autosomal recessive RP (arRP), and 6 genes in X-linked RP (xlRP), causing different RP phenotypes. Characteristically, *RHO* is the most prevalent adRP- and arRP-causing gene, and *RPGR* the most common xlRP-causing gene. Other important genes are *PRPH2*, *RP1*, *CRX*, *RPE65*, *ABCA4*, *CRB1*, and *USH2A*. However, different phenotypes can also be caused by mutations in the same gene.
Conclusions: The genetic heterogeneity of RP necessitates further study to map the exact mutations that cause more severe forms of RP, and to develop and use appropriate genetic or other effective therapies in future.

KEY WORDS

retinitis pigmentosa, genes, syndromic RP, non-syndromic RP, retinal dystrophy, genetics, Bardet–Biedl syndrome, autosomal dominant, heterogeneity, RP, photoreceptor, Usher syndrome, autosomal recessive RP

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INTRODUCTION

Retinitis pigmentosa (RP) is an inherited eye disease that manifests with various dystrophic and degenerative symptoms. It is thought to be the most common type of retinal dystrophy [1-5], and affects millions of individuals worldwide, including over 200,000 individuals in the USA [6, 7]. RP was first described by Van Trigt in 1853 (through an ophthalmoscope) and was recognized as a pathological condition by Donders, 4 years later [7]. Although retinitis

involves inflammation of the retina, RP refers to a hereditary condition without inflammation [8].

Degeneration of rods and cones, and of the retinal pigment epithelium (RPE) is typical of RP disorders. The degeneration usually develops at the middle (50° to 90°) of the periphery of the retina and progresses towards the central region of the retina, frequently affecting the macula and fovea [2, 5-7]. Clinically, it differs from other retinal diseases, such as Leber congenital amaurosis (LCA), macular dystrophies (MD), and cone–rod dystrophies (CRD), which are inherited retinal diseases (IRDs) that present at birth or early in postnatal life. It is also clinically distinct from non-progressive conditions, including achromatopsia and congenital stationary night blindness (CSNB) [7]. There are several other ocular conditions associated with RP. Refractive error or nystagmus may occur in early-onset RP, whereas macular hole, epiretinal membrane formation, and cystoid macular edema (CME) may be present in more than 50% of RP patients. In addition, posterior subcapsular cataracts are present in up to 45% of RP patients, secondary retinal vasoproliferative tumors, vitreous cysts in 6% of RP patients, and optic nerve head and fiber layer drusen in approximately 9% of RP patients [7].

The present review sought to present the various types of RP, and the symptoms and retinal findings that appear progressively at each stage of the disease. In addition, we review the genetic heterogeneity of RP, referring to the genes most commonly implicated in different forms of the disease. We also analyze the clinical manifestations of disease-causing mutations of the most important pathogenic genes.

METHODS

We screened the PubMed/MEDLINE and Google Scholar databases for articles referring to clinical manifestations and genes related to both syndromic and non-syndromic RP. The present review focused on articles in the English language published between January 2008 and February 2020. Keyword combinations of “retinitis pigmentosa,” “genetics,” “genes“, and “(non) syndromic“ were used.

RESULTS

In total, 105 articles were analyzed, with a focus on the most recent literature. Further bibliographic research on the reference list of these articles revealed another 34 related articles that were also analyzed and included in the review. Based on the reviewed literature, this article focuses on the types and clinical manifestations of RP, and summarizes the key genes and disease-causing mutations associated with the pathogenesis of syndromic and non-syndromic RP. Table 1 summarizes the genes reported to date as causes of Usher syndrome. Table 2 summarizes the genes reported to cause Bardet–Biedl syndrome (BBS) in the current literature. Table 3 summarizes the genes reported to cause autosomal dominant (ad) RP in the current literature. Table 4 summarizes the genes reported to cause autosomal recessive (ar) RP in the current literature. Table 5 summarizes the overlap between genes causing RP and causing other IRDs, and Table 6 summarizes all abbreviations used in the text.

DISCUSSION

TYPES OF RP

Non-syndromic RP: Symptoms and retinal findings

RP may occur alone without other clinical manifestations, and is then known as non-syndromic RP, or it may occur along with developmental abnormalities, neurosensory disorders, or various combined clinical phenotypes, and is then known as syndromic (or systemic) RP [9]. Approximately 70–80% of all RP cases are non-syndromic. The worldwide prevalence of RP in patients without systemic manifestations is estimated to be 1 in 4000 [1-4, 9, 10], although it ranges from 1:9000 to 1:750, depending on the geographic location [7]. For instance, it is estimated to be 1:3800 in China [1].

Non-syndromic RP is inherited in an ad form (adRP; 20–40%), ar form (arRP; 30–50%), or in an X-linked form (xlRP) (5–15%) [1-4, 9, 11]. Non-Mendelian inheritance patterns accounts for only a minor proportion of cases. These include digenic, mitochondrial, and de novo mutations [3, 4, 9, 11, 12]. In addition, approximately 30% of all non-syndromic RP cases are sporadic, while most exhibit an apparently autosomal recessive inheritance [1, 3, 12]. However, these percentages vary among populations [3].

XlRP appears to be the most severe form of RP, as it progresses more aggressively and is characterized by early-onset. Clinically, it is more severe in men than in women [10]. AdRP cases are characterized by the best long-term prognosis in terms of retaining central vision [7]. In a previous report, by the age of 20 years, 87% of patients with xlRP and 75% of patients with adRP had symptoms, whereas this proportion was only 61% for arRP and 64% with simplex cases. By the age of 30 years, all xlRP patients, 89% of adRP patients, 74% of arRP patients, and 79% of simplex cases presented with symptoms [8].

Hence, adRP has been reported to have the best prognosis, whereas xlRP is the most aggressive form, and in xlRP all patients aged 50 years and older have a visual acuity worse than 20/200. In addition, intermediate severity is present in patients with arRP. However, other reports suggest that genetic subtypes do not affect central visual impairment [8].

Syndromic RP

Approximately 20–30% of RP cases present with systemic manifestations. Syndromic RP appears in more than 30 different syndromes. Overall 20–40% of these cases are inherited in a recessive manner and 10–20% appear in conjunction with Usher syndrome [9]. It is a major cause of combined deafness and blindness, and is responsible for approximately 50% of all cases with these symptoms. It affects 1:12,000 to 1:30,000 individuals in different populations and has a prevalence of 5–6 per 100,000 individuals in the USA and Northern Europe [12, 13].

It is divided into three types. Type I, which is present at birth, is the most severe form, and is characterized by progressive hearing loss and is associated with vestibular ataxia. Type II, which is non-progressive, congenital, and mild to moderate in severity, presents with retinal degeneration in older age, but without vestibular dysfunction. Type III, which is progressive, with normal hearing present in youth and with gradual hearing loss during later years [9, 12, 13]. Mental and behavioral disorders, including schizophrenia-like psychosis, have also been reported in Usher patients [13]. There are 12–15 genes that can cause Usher's syndrome, with different mutations causing each type, while some mutations may cause either RP without hearing loss or deafness without RP [9]. Genes implicated in type I Usher syndrome are *MYO7A* (USH1B; 11q13.5), *CDH23* (USH1D; 10q22.1), *PCDH15* (USH1F; 10q21.1), *USH1C* (USH1C; 11p15.1), *USH1G* (USH1G; 17q25.1), *CIB2* (15q25.1), and *CLRN1* (3q25.1). Those involved in type II are *USH2A* (USH2A; 1q41), *GPR98* (USH2C; 5q14.3), and *DFNB31* (USH2; 9q32). Genes involved in type III are *HARS* (USH3A; 5q31.3), and *ABHD12* (2p11.21) [12, 14]. Table 1 summarizes the genes reported to date as causes of Usher syndrome.

Bardet–Biedl syndrome (BBS) is a syndrome that may involve syndromic RP. It is characterized by a fundus abnormality with early macular involvement, consisting of a non-typical pigmentary retinal dystrophy. BBS accounts for as many as 5–6% of RP cases [9]. The prognosis for affected children is poor, as legal blindness appears at the age of 15.5 years. Night blindness is also observed in the first decade. BBS is associated with kidney disease, polydactyly, obesity, renal dysfunction, hypogonadotropic hypogonadism (in male patients), genitourinary malformations (in female patients), cognitive impairment, and developmental delay. Mortality is frequently associated with renal disease, which is inherited in an autosomal recessive pattern, affecting 1:120,000 Caucasians [12]. Mitochondrial diseases or degenerative cerebellar diseases may also be associated with BBS pathogenesis [6, 7]. These manifestations vary in BBS patients depending on the gene and the exact mutation implicated in BBS pathogenesis in each individual [7]. Twenty one genes have been identified in BBS, including *BBS1* (11q13; implicated in 40% of BSS patients), *BBS2* (16q12.2; implicated in 20% of BSS patients), *ARL6* (causing BBS3; 3q11.2), *BBS4* (15q24.1; implicated in 3–6% of BSS patients), *BBS5* (2q31.1; implicated in 2% of BSS patients), *MKKS* (causing BBS6; 20p12.2), *BBS7* (4q27), *TTC8* (causing BBS8; 14q32.11), *B1* (causing BBS9; 7p14.3), *BBS10* (12q21.2), *TRIM32* (causing BBS11; 9q33.1), *BBS12* (4q27), *MKS1* (causing BBS13) (17q22), *CEP290* (causing BBS14; 12q21.32), *BBIP1* (10q25.2), *IFT27* (22q12.3), *INPP5E* (9q34.3), *KCNJ13* (2q37.1), *LZTFL1* (3p21.31), *NPHP1* (2q13), and *SDCCAG8* (1q43) [12, 14]. These genes cause approximately 70% of cases, and most of the mutations are associated with autosomal recessive patterns of inheritance [9]. Further BBS-associated genes are yet to be identified, as approximately 30% of BBS cases are not associated with any of the 21 genes reported to date [12]. Table 2 summarizes the genes reported to cause BBS in the current literature. Other clinically important syndromic forms of RP are Bassen–Kornzweig syndrome (abetalipoproteinemia), Refsum's disease (phytanic acid oxidase deficiency), and α-tocopherol transport protein deficiency (vitamin E deficiency) [9].

Table 1. Genes Reported to Cause Usher Syndrome

Gene	Chromosome
ABHD12 **(Abhydrolase Domain Containing 12, Lysophospholipase)**	2p11.21 [13]
CDH23 **(Cadherin Related 23)**	10q22.1 [12, 13]
CIB2 **(Calcium And Integrin Binding Family Member 2)**	15q25.1 [13]
CLRN1 **(Clarin 1)**	3q25.1 [13]
DFNB31 **(Deafness, Autosomal Recessive 31)**	9q32 [12, 13]
GPR98 **(G Protein-Coupled Receptor 98)**	5q14.3 [12, 13]
HARS **(Histidyl-TRNA Synthetase)**	5q31.3 [13]
MYO7A **(Myosin VIIA)**	11q13.5 [12, 13]
PCDH15 **(Protocadherin Related 15)**	10q21.1 [12, 13]
USH1C **(USH1 Protein Network Component Harmonin)**	11p15.1 [12, 13]
USH1G **(USH1 Protein Network Component Sans)**	17q25.1 [12, 13]
USH2A **(Usherin)**	1q41 [12, 13]

Symptoms of RP

RP results in progressive vision loss and blindness [1]. The age of onset ranges from early childhood to mid-adulthood [15]. Problems with dark adaptation often manifest during adolescence, while visual loss in the mid-peripheral field is usually evident in the second and third decades of life. Despite this general rule, the age of onset varies among patients. Early onset RP usually progresses more rapidly. Some patients therefore develop visual loss by the age of 30, while others remain asymptomatic until the fifth decade of life [7]. The diagnosis of early-onset RP is based on the presence of mid-stage RP symptomatology after the age of 2 years. However, the diagnosis of late-onset RP requires that the first symptoms of RP present in midlife or later [5, 6].

Nevertheless, it is difficult to determine the age of RP onset accurately, because many patients, and particularly children, compensate for the loss of peripheral vision. In addition, the artificial illumination of nighttime environments tends to mask possible problems with dark adaptation [7]. In extreme cases, RP progresses rapidly over the course of two decades. At the other extreme, the disease may present with slow progression and may never lead to blindness [5]. RP is a very common cause of visual impairment in patients aged 30–60 years, with higher parental consanguinity than other genetic diseases, such as Stargardt disease (STGD) and retinopathy of prematurity [16].

Typically, RP is present during the first years of life. However, it may also appear in early adolescence or even later in life. Often, night blindness is not evident in young patients, and only becomes apparent between 12 and 18 years old. There are also defects in the visual field in dim light, whereas minor defects appear in visual acuity, and color vision is normal. Thus, it is difficult to diagnose RP at an early stage, as symptoms may not yet have manifested, particularly in cases where there are no other family members affected with RP. Scotopic visual fields present scotomas and electroretinograms (ERGs) may be normal when RP has not yet progressed, while a decreased amplitude of the b-wave on ERG may be present in dark conditions [5-7].

In the mild stages, night blindness is obvious; there is loss in the peripheral visual field under photopic conditions, dyschromatopsia, particularly in terms of blue and yellow, and photophobia in diffuse light. Visual acuity is decreased, as macular involvement may also be present, or because of subcortical posterior cataract, which should be removed even in the presence of macular involvement. Atrophy of the retina is evident upon fundus examination at this stage, along with minute bone spicule-shaped pigment deposits at the middle periphery. The retinal vessels appear narrow, while the optic disc is rather pale. Scotopic ERG (rods), in most cases, cannot be recorded. ERG cone responses are markedly diminished. Mild peripheral scotomas are evident in visual field tests, frequently progressing to the extreme periphery or the macula [5-7].

Table 2. Genes Reported to Cause Bardet-Biedl Syndrome

Genes	Chromosome
ARL6 **(ADP Ribosylation Factor Like GTPase 6)**	3q11.2 [12, 13]
BBIP1 **(BBSome Interacting Protein 1)**	10q25.2 [13]
BBS1 **(Bardet-Biedl Syndrome 1)**	11q13 [12, 13]
BBS2 **(Bardet-Biedl Syndrome 2)**	16q12.2 [12, 13]
BBS4 **(Bardet-Biedl Syndrome 4)**	15q24.1 [12, 13]
BBS5 **(Bardet-Biedl Syndrome 5)**	2q31.1 [12, 13]
BBS7 **(Bardet-Biedl Syndrome 7)**	4q27 [12, 13]
BBS9 **(Bardet-Biedl Syndrome 9)**	7p14.3 [12, 13]
BBS10 **(Bardet-Biedl Syndrome 10)**	12q21.2 [12, 13]
BBS12 **(Bardet-Biedl Syndrome 12)**	4q27 [12, 13]
CEP290 **(Centrosomal Protein 290)**	12q21.32 [12, 13]
IFT27 **(Intraflagellar Transport 27)**	22q12.3 [13]
KCNJ13 **(Potassium Inwardly Rectifying Channel Subfamily J Member 13)**	2q37.1 [13]
LZTFL1 **(Leucine Zipper Transcription Factor Like 1)**	3p21.31 [13]
NPHP1 **(Nephrocystin 1)**	2q13 [13]
MKKS **(McKusick-Kaufman Syndrome)**	20p12.2 [12, 13]
MKS1 **(MKS Transition Zone Complex Subunit 1)**	17q22 [12, 13]
TRIM32 **(Tripartite Motif Containing 32)**	9q33.1 [12, 13]
TTC8 **(Tetratricopeptide Repeat Domain 8)**	14q32.11 [12, 13]
SDCCAG8 **(SHH Signaling And Ciliogenesis Regulator SDCCAG8)**	1q43 [13]

The end stage of RP is characterized by the inability of RP patients to move autonomously because of peripheral vision loss and classic tunnel vision. Reading is difficult or impossible, photophobia is severe, ERG is unrecordable, and fundus examination reveals pigment deposits in the central retina, particularly the macula. The optic disc appears to have a waxy pallor, and the retinal vessels are thin. Chorioretinal atrophy is evident on fluorescein angiography, both at the periphery and at the foveomacular area [5-7].

Hence, nyctalopia and difficulties in adapting to changes in brightness may be present in the early stages of RP [1, 5, 9]. This is considered to be the earliest symptom of RP [5] which, eventually, develops into "tunnel vision" (loss of peripheral vision) and, finally, legal or complete blindness [2, 5-7, 9]. The loss of photoreceptors in the outer retina, the rods that mediate vision at night and generally scotopic conditions, and the cones that mediate color vision and vision under generally photopic conditions may cause several visual symptoms. On the other hand, cells in the inner retina, including bipolar cells, amacrine cells, and ganglion cells, are affected later [9].

Most frequently, nyctalopia usually starts in the first decade of life, while peripheral visual field defects are present in the second decade of life and, in most cases, by the fourth or fifth decade of life, visual acuity is completely lost. Nevertheless, the course of RP in female carriers is characterized by variable clinical symptoms, and visual impairment usually appears in early middle age [10]. Anatomical defects of the central retina may manifest early during the progression of the disease. However, the central retina and function of the macula are relatively free until the late stages of the disease. Eventually, cone degeneration causes poor visual acuity until the fourth decade of life, although most patients retain the ability to perceive light. This is associated with residual macular function [7].

As already mentioned, another characteristic feature of RP is the progressive loss of the visual field, presenting with bilateral symmetry and beginning with scotomas in the mid-peripheral areas. These isolated scotomas gradually coalesce into an annular scotoma that extends both in the outward and inward directions. In addition, progression of concentric visual field loss, which follows an arcuate pattern and proceeds in the superior to inferior direction of the retina, has been reported [7, 9].

Another common but often-neglected symptom of RP is photopsia. It can occur early in RP progression, but it may be highly disturbing in advanced RP. Photopsia may result from the absence of afferent nerve impulses due to photoreceptor degeneration or may be the result of spontaneous self-signaling due to inner retinal remodeling [5, 7].

In addition, other symptoms that characterize RP patients are photophobia [5, 7], myopia, and hyperopia. Both myopia and hyperopia, particularly high forms, are also more prevalent in patients with RP. Hyperopia among RP patients mostly appears with mutations in *CRB1*, *NR2E3*, or *LRAT*. In contrast, myopia is more related to Usher syndrome. It is also associated with the *RBP3*, *ZNF408*, and *RP1* genetic subtypes in arRP and with the *RP2* and *RPGR* genetic subtypes in xlRP [7].

At the cellular level, RP is a progressive disability resulting from the loss of rods. In the beginning, it compromises night vision by affecting the mid-peripheral retina, which has abundant rod photoreceptors. Subsequently, it progresses into the central retina, eventually eliminating cones either directly due to the disease process or indirectly through rod death [6, 7]. Finally, the disease onset, progression, retinal appearance (i.e., rod versus cone involvement, involvement of the RPE and other types of retinal cells, such as bipolar cells), secondary symptoms (e.g., CME), and final visual outcome vary widely, even among blood relatives [1, 3, 6, 7].

Retinal findings of RP

Upon examination, the main retinal manifestations include bone-spicule formations and thinning of blood vessels, a waxy pallor of the optic nerve, and changes in structure. Shortening of the photoreceptor outer segments (OSs) imaged by optical coherence tomography (OCT), reduced visual fields, and reduced and/or abnormal ERG [1, 2, 6, 10, 11], such as the amplitude diminution of a- and b-waves are paraclinical manifestations of RP [5]. This indicates characteristic loss mostly of rod photoreceptor function in the early stages of RP [7]. OCT, visual field examination, and ERG are non-invasive procedures that are not time-consuming and can be easily performed, even in adolescents. In particular, OCT and full-field ERG (ffERG) provide objective and detailed information about central retinal structure and function. Such information contributes to both the detection and identification of the clinical phenotype of RP [17].

In the early stages, vascular thinning is minimal, bone-spicule formations are, at most, sparse, and the optic disc is mostly normal in appearance; thus, a fundus examination may appear normal. In addition, some RP patients may have non-specific abnormalities, such as broadening of the foveal reflex, irregular reflexes from the internal limiting membrane, or whitish lesions. However, some patients develop dust-like pigmentation, while

others develop nummular hyperpigmentation, which may vary among patients, without reflecting the severity of the disease. Melanin pigment deposits are formed by RPE cells with bone-spicule pigmentation, which are detached from Bruch's membrane after photoreceptor degeneration and intraretinal migration. Bone-spicule formations are most often evident in the rod-rich mid-periphery [5, 7].

Vascular thinning in the retina of RP patients seems to be the result of photoreceptor loss, leading to reduced metabolic demand. An alternative explanation is that it is the result of a hyperoxic state of the inner retina, provoking loss of oxygen-consuming photoreceptors, leading to retinal vessel thinning and reduced blood flow. A third explanation suggests that vessel narrowing is caused by thickening of the extracellular matrix, where the vessels are embedded together with the RPE cells that have migrated [7].

Moreover, vascular remodeling and subsequent vessel attenuation are attributed to the decreased metabolism of the inner retinal layers [7]. Other studies suggest that retinal atrophy is associated with a reduction in ocular blood flow [5, 7]. Thus, it remains unclear whether RP-associated vascular changes are secondary to neuroretinal remodeling or whether they are of primary importance for RP development. Additionally, the vasoconstrictor endothelin-1 may be involved in RP development. Finally, the waxy pallor, which typically develops in the optic disc, is due to the glial cells situated either on the surface or inside the optic disc, causing enhanced light reflectance [7].

GENETIC ASPECTS OF RP PATHOGENESIS

Genes associated with RP pathogenesis

The term IRDs includes several different diseases, with more than 190 genes involved in some form of IRD [6, 18]. RP seems to be associated with dozens of different genetic defects [7]. Hence, at a genetic level, RP is thought to be complicated and heterogeneous [1, 2, 10], while it accounts for approximately half of IRD cases. Non-syndromic RP has been associated with more than 80 genes [3, 6, 7], whereas approximately 30 genes may cause syndromic RP, such as that seen in Usher syndrome and BBS [2].

Genes that are associated with RP belong to several groups. These include genes encoding proteins that convert a photon into a neuronal signal, a procedure important for normal vision, including rhodopsin (*RHO*), *PDE6A*, and *PDE6B*, which encode proteins of the visual cycle that recycle the chromophore of rhodopsin. Other genes encode tetraspanins, are structural photoreceptor proteins; photoreceptor cell transcription factors that enhance the expression of photoreceptor genes, including *NRL* and *CRX*. Additionally, some genes are involved in the regulation of catabolic functions in the retina, mitochondrial genes that are involved in mitochondrial metabolism, and several other categories. Moreover, there are genes with unknown functions that contribute to the progress of RP, such as *RP1*, *RP2*, *RP3* (RP GTPase regulator, *RPGR*), *RP12* (*CRB1*), and *RP14* (*TULP1*) [19].

Hence, most genes encode proteins that are vital for the neuroretina and/or RPE, or some underlying structure. Thus, depending on the gene mutation, impaired or disrupted pathways may be caused. The first gene to be identified in adRP is *RHO*. Subsequently, several new genes have been implicated in RP pathogenesis. Each of these is associated with a specific RP subtype, which, in turn, is characterized by typical progression, age of onset, symptomatology, and retinal appearance. Several genes, such as *CWC27*, *IMPDH1*, and *CRX*, are related to early-onset RP, whereas others, such as *HGSNAT*, *CRX*, and *RBP3* are associated with late-onset RP [7].

A great many mutations in these genes are implicated in RP pathogenesis. There are more than 3100 mutations in non-syndromic RP genes alone [2, 3, 6, 20]. Syndromic RP is equally heterogeneous [6] and represents 20-30% of RP cases [7]. . As mentioned above, mutations in 12–15 genes may be implicated in Usher syndrome pathogenesis and 21 genes with BBS pathogenesis [14]. Another 1200 pathogenic mutations have been implicated in these syndromes. Apart from the genetic heterogeneity that they entail, various overlapping diseases and symptoms may be caused by mutations in the same gene. At the same time, there is great variation in their clinical expression. This variability manifests itself even among patients presenting with the same mutation in the same gene [6]. Within each subtype, various factors play a crucial role, indicating that the RP phenotype may be affected by genetic and environmental factors [7].

To date, approximately 27 adRP, 55 arRP, and 6 xlRP genes have been identified in the Genecards and RetNet databases [1, 11, 14]. Some genes can cause both adRP and arRP, such as *RHO*, *BEST1*, *NRL*, *IMPDH1*, *NR2E3*, *RP1*, and *RPE65* [1, 21], while others can cause both RP and macular degeneration (MD), such as *ABCA4*, *PROM1*, *PRPH2*, *C8orf37*, and *PRPF31* [1]. In addition, some genes have been implicated in both RP and LCA (*CRB1, RPE65, CRX, LRAT, IMPDH1, PRPH2, SPATA7, RDH12,* and *TULP1*) and others in both RP and cone dystrophy (CD)/CRD (*CRX, C8orf37, PRPH2, PROM1, ABCA4, CERKL, SEMA4A,* and *RPGR*) [2, 6].

The most prevalent genetic causes of adRP are *RHO*, which causes approximately 26% of cases, *RP1*, which causes 6%

of cases, and the gene for pre-mRNA processing factor 31, *PRPF31*, which causes 5% of adRP in the United States. In Europe, the prevalence is lower for mutations in *RHO* (16.5%) and higher for mutations in *PRPF31* (6.7%) [17]. Other mutated genes associated with adRP are *SPP2* (2q37.1), *BEST1* (11q12.3), *CRX* (19q13.32), *OR2W3* (1q44), *HK1* (10q22.1), *TOPORS* (9p21.1), GUCA1B (6p21.1), *NRL* (14q11.2), *NR2E3* (15q23), *SEMA4A* (1q22), *FSCN2* (17q25.3), *RHO* (3q22.1), *CA4* (17q23.2), *PRPH2* (*RDS*) (6p21.1), *RPE65* (1p31.2), *PRPF8* (17p13.3), *ROM1* (11q12.3), *PRPF31* (19q13.42), *IMPDH1* (7q32.1), *KLHL7* (7p15.3), *RP1* (8q12.1), *PRPF4* (9q32), *PRPF3* (1q21.2), *RDH12* (14q24.1), *PRPF6* (20q13.33), *RP9* (7p14.3), and *SNRNP200* (2q11.2) [12, 20]. It is estimated that among different populations, 50–75% of RP cases are associated with adRP gene mutations [20]. However, some of these mutations, at a later time, may be proven to be nonpathogenic, whereas other novel mutations that have not yet been identified may be discovered [6]. Table 3 summarizes the genes reported to cause adRP in the current literature.

In contrast, there are approximately 55 genes implicated in arRP. The following cause up to 2–5% of cases: *RPE65* (1p31.2), *PDE6A* (5q33.1), *PDE6B* (4p16.3), and *RP25*. Other genes implicated in arRP are *ADIPOR1* (1q32.1), *POMGNT1* (1p34.1), *ZNF408* (11p11.2), *NEUROD1* (2q31.3), *IFT172* (2p33.3), *IFT140* (16p13.3), *HGSNAT* (8p11.21), *RDH11* (14q24.1), *DHX38* (16q22.2), *KIZ* (20p11.23), *BEST1* (11q12.3), *ABCA4* (1p22.1), *ARL2BP* (16p13.3), *C2orf71* (2p23.2), *C8Oorf37* (8q22.1), *CERKL* (2q31.3), *CLRN1* (3q25.1), *CNGA1* (4p12), *CNGB1* (16q13), *CRB1* (1q31.3), *DHDDS* (1p36.11), *DHX38* (16q22.2), *EMC1* (1p36.13), *EYS* (6q12), *FAM161A* (2p15), *GPR125* (4p15.2), *IDH3B* (20p13), *IMPG2* (3q12.3), *KIAA1549* (7q34), *KIZ* (20p11.23), *LRAT* (4q32.1), *MAK* (6p24.2), *MERTK* (2q13), *MVK* (12q24.11), *NEK2* (1q32.3), *NR2E3* (15q23), *NRL* (14q11.2), *PDE6G* (17q25.3), *PRCD* (17q25.1), *PROM1* (4p15.32), *RBP3* (10q11.22), *RGR* (10q23.1), *RHO* (3q22.1), *RLBP1* (15q26.1), *RP1* (8q12.1), *SAG* (2q37.1), *SLC7A14* (3q26.2), *SPATA7* (14q31.3), *TTC8* (14q32.11), *TULP1* (6p21.31), *USH2A* (1q41), *ZNF513* (2p23.3) [12, 14]. Table 4 summarizes the genes reported to cause arRP in the current literature.

Six gene loci, mapped to the X-chromosome, have been implicated in xlRP pathogenesis: *RPGR* (Xp11.4), *RP2* (Xp11.23), *RP6* (Xp21.3-p21.2), *OFD1-RP23* (Xp22.2), *RP24* (Xq26-q27), and *RP34* (Xq28-qter), the product of at least two of which have been identified: RPGR or RP3 and the RP2 protein (RP2) [6, 18]. It seems that *RPGR* mutations are responsible for approximately 70–90% of xlRP cases and more than 20% of all RP cases, while 6–20% of xlRP cases are caused by *RP2* mutations. In particular, *RPGR* is thought to be one of the most significant RP genes as it impacts central vision and appears at a high incidence [18]. Although, 30–60% of all xlRP cases are associated with the ORF15 region, only 20% of RP3 mutations are present in *RPGR* coding exons. Thus, more than 80% of clinical cases are associated with *RPGR* and *RP2*. Hence, gene therapy and small-molecule drugs may focus on these genes [12].

Interestingly, although the RP genes are universal, new mutations appear at roughly the same rate worldwide, and there are differences in the prevalence among different populations. For example, *RHO* mutations are responsible for 30% of adRP cases in Americans of European origin, but only 10% of such cases in China. This is thought to be due to the absence of the Pro23His mutation in China. On the other hand, the prevalence of other gene mutations, such as that of mutations in *RPGR*, is roughly the same worldwide [20].

Genetic diagnosis of RP

The functions of many genes have been extensively studied, but there is partial overlap of the clinical phenotypes of a number of these. Thus, it is necessary to discover accurate genotype–phenotype correlations. Two main methods have been used for genetic diagnosis of IRD. Either specific genotyping microarrays are used which, depending on the IRD form, detect 11–70% of mutations, or Sanger sequencing is used for mutation screening [3].

Several methods have been used to detect disease-causing mutations, such as deletion detection, linkage mapping, and subclone sequencing of *RPGR* ORF15 [20].

Given that a precise prognosis of the symptomatology and appropriate genetic counseling are necessary for the correct management of IRDs, the molecular diagnosis of the IRD is of paramount importance. Important information may be provided by the molecular characterization of IRD-affected patients for the potential use of gene therapy. In addition, the development of new technologies, such as next-generation sequencing (NGS), has enabled the analysis of dozens of genes. This technique provides an easier molecular diagnosis of IRD, as it is characterized by high sensitivity and efficiency despite the heterogeneous nature of IRDs. NGS is thought to be very accurate in screening gene mutations and hence may be used efficiently as a diagnostic tool [3].

Three advanced technologies are using NGS, each with advantages and disadvantages: targeted retinal-gene capture NGS, whole-exome NGS, and whole-genome NGS. However, the present limitations of the NGS methods curb

their ability to detect insertions, deletions, and variable-length repetitive elements [20].

As already mentioned, gene therapy may be used widely in future, based on efficient and accurate diagnosis of the disease and disease-causing mutations. However, RP management may also be based on new approaches for cell replacement. Transplantation of stem cells may provide better vision in patients with RP. In addition, stem cells could restore structures of the retina that are affected in these patients, particularly when used at the appropriate time and stage of the disease. Previous animal studies on the use of stem cells, which can differentiate into retinal cells and progressively develop features of new cells, have shown encouraging results. However, future studies must optimize these approaches for their use in humans [22].

Oxidative stress may also be a causative factor of various retinopathies, including RP, as it may enhance the death of photoreceptor cells. On the other hand, in the early stages, increased intake of lutein, an important antioxidant, may provide satisfactory protection to the retina and the macula, particularly in predisposing individuals. This emphasizes the need for early diagnosis. Similar protection of the retina and photoreceptors has been attributed to anthocyanins [23].

The aim of molecular studies is to facilitate accurate genetic testing in RP patients, to provide information for use in clinical care and counseling. Additionally, new treatments based on improved understanding of disease pathogenesis will be developed. However, to attain this target, close cooperation between retinal specialists, genetic counselors, molecular geneticists, and bioinformatics experts is needed [20].

The extremely high heterogeneity of RP has led to many attempts to analyze and map the genes that contribute to the appearance and progression of several types of RP [6, 12, 14]. Below, some of the most important genes involved in adRP, arRP, xlRP, and digenic RP are discussed.

SPECIFIC GENES INVOLVED IN RP PAHOGENESIS

RHO

RHO (*RP4*, Opsin-2) is located on chromosome 3q22.1 and encodes the rod-specific protein, rhodopsin, which belongs to the G protein-coupled receptor (GPCR) family [6, 11, 24, 25]. Rhodopsin is produced in the inner segment (IS) of rods and is transported to the outer segment (OS) of the rods. It is a visual pigment that mediates vision in dim light, and it begins the visual transduction cascade [11].

The protein is composed of 348 amino acids, with seven transmembrane domains, a luminal N terminus, and a cytoplasmic C-terminus. The activation of rhodopsin protein is controlled by the 11-cis-retinal attachment site (Lys296), which is found in the seventh transmembrane domain [11].

RHO is known as the “major” gene of adRP [2, 4, 6, 24, 25]. It is also defined as *RP4* and is responsible for about 20–30% of all adRP cases. More than 150 mutations in *RHO* have been identified as causing RP. The first RP causative gene defect in *RHO* was p.P23H, which is implicated in approximately 12% of USA RP patients [11, 19].

Additionally, mutations in this gene are responsible for arRP. However, only a few arRP-causing mutations have been identified in *RHO* [11, 19], which are also associated with adCSNB [2, 6]. The prevalence of *RHO* mutations in adRP has been estimated to range from 16% to 35% in Western populations. In the Israeli and Palestinian populations, *RHO* mutations are also a significant cause of adRP [26]. Disease-causing mutations have also been identified in Spanish [27], Iranian [28], Japanese 29, and Korean [30] families with adRP. In Swedish families, mutations in *RHO* are associated with phenotypic intrafamilial variability and more severe phenotypes in younger generations [17]. For arRP, *RHO* mutations have been identified most frequently in Chinese families, The p.P347L mutation is the most common *RHO* mutation in China and is also a significant RP-associated mutation worldwide [11].

Finally, as *RHO* is a major causative gene in adRP, many therapies targeting *RHO* have been attempted in experimental animals. Moreover, the use of gene-corrected autologous induced pluripotent stem cells (iPSCs) has been suggested for treating adRP patients [11].

PRPH2/RDS and *ROM1*

PRPH2 is located on chromosome 6p21.1. This gene is also known as retinal degeneration slow/RDS [27]. It contains three exons and encodes peripherin 2, an integral membrane glycoprotein of 39-kDa, which is composed of 346 amino acid proteins [2, 6]. This protein contains one intradiscal domain (D2) and four transmembrane domains (M1–M4) [31]. *ROM1*, which encodes rod outer-membrane protein 1, along with RDS, encodes structural proteins of the photoreceptors; hence, it is important for the development and function of rods and cones. These proteins form heterotetramers in rod OS discs. *ROM1* and *PRPH2* encode proteins of the tetraspanin superfamily, which include four-transmembrane-domain proteins [19]. Tetraspanins, as a family, contribute to the development of several signaling pathways and are associated with many different molecules. However, the heterogeneity of symptomatology in RP patients with either *PRPH2* or *ROM1* mutations indicates that another interacting protein is probably involved. Prominin like-1 (PROM-1) is

probably responsible for these interactions. It is a five-transmembrane-domain protein localized to rod OS discs. *PROM1* is mutated in autosomal recessive retinal degeneration [19].

PRPH2 is thought to be a significant causative gene of adRP and CRD [27, 32-34]. Disease-causing mutations in *PRPH2* are related to both adRP and adMD [1, 6, 35]. *PRPH2* may be responsible for adSTGD1-like phenotypes [36], whereas a few dominant adult onset vitelliform macular dystrophy (AVMD) patients also carry mutations in *PRPH2* [2, 37, 38]. It may also be related to secondary defects in neighboring tissues, including the choroid and RPE [31]. Thus, mutations in *PRPH2* may be a direct cause of RP [19]. Over 151 *PRPH2* mutations have been identified, many of which have been confirmed to be pathogenic. However, *PRPH2*-associated disease phenotypes display substantial variability, even among blood relatives carrying the same mutation [31].

Mutations in *ROM1* are not clearly linked to monogenic adRP [31]. However, an uncommon form of RP is autosomal digenic RP, which involves heterozygous mutations in both *ROM1* and *PRPH2* [2, 6, 39]. However, cases have been reported where RP is caused by *ROM1* mutations in the absence of *PRPH2* mutations, whereas *PRPH2* mutations have also been reported in several macular pattern dystrophies [19]. The question that has been pursued is how different mutations give rise to differences in disease phenotypes [40-42], but as of yet, this remains unclear. Many of the genes associated with retinal disease can potentially modify *PRPH2*-associated phenotypes. Among them, *ROM1* is the most widely explored gene, due to the existence of *PRPH2*/*ROM1* digenic RP and ROM1 interaction with PRPH2. However, other genes have also been implicated in modifying the *PRPH2*-associated MD phenotype, including *ABCA4* [31].

The prevalence of adRP-related *PRPH2* mutations varies widely according to the populations studied, ranging from 0% in Mexican populations to 10.3% in French populations [24, 43]. *PRPH2* is the second most common cause of adRP after *RHO,* in the French population. Moreover, *PRPH2* mutations were found in 4.7% of a Belgian cohort. *PRPH2* mutations are associated with highly variable phenotypes. These include moderate and mild forms of adRP. Mild forms can, at times, be underdiagnosed [43]. Most *PRPH2* mutations are sequence variants. Aberrant mRNA splicing, problems in protein localization, and protein degradation are some of the mechanisms which may result in decreased PRPH2 protein expression in rod OS [24].

PRPF3*, *PRPF4*, *PRPF6*, *PRPF8*, *PRPF31,* and *SNRNP200

PRPF3, *PRPF4*, *PRPF6*, *PRPF8*, and *PRPF31* encode pre-RNA processing factors 3, 4,6, 8, and 31, respectively [2]. Of these, *PRPF3*, *PRPF8*, and *PRPF31*, together with *SNRNP200*, are the major causative genes of RP. Indeed, the U4/U6-U5 tri-snRNP complex is composed of PRPF3, PRPF8, PRPF31, and SNRNP200 and is a major component of the spliceosome that participates in mRNA splicing [4, 27, 44, 45]. More specifically, *SNRNP200* encodes helicase hBrr2, a 200-KDa protein. Helicase hBrr2, together with several other RNA helicases, mediates the structural rearrangement of the spliceosome, permitting the unwinding of the U4/U6 snRNP duplex, and activating the catalytic properties of the spliceosome complex [4]. Both heterozygous and homozygous variants of this gene cause RP [46]. Approximately 38% of adRP patients showed mutations mainly in *SNRNP200* and *PRPF8* [4]. *PRPF4* and *PRPF6* mutations also cause adRP, albeit less frequently. All tissues in all eukaryotes express *PRPF4* and *PRPF6* [2]. *PRPF4* encodes HPrp4, which is essential for continuous splicing. It has been reported that this gene co-segregates with the adRP disease phenotype in a Chinese family [47]. *PRPF31* is located on 19q13.42 [2]. It is composed of 14 exons and encodes a 499-amino acid protein that is implicated in spliceosome function. It binds to U4 small nuclear ribonucleoprotein (snRNP) in U4/U6 di-snRNP and contributes to the development of a connection between U5 and U4/U6 di-snRNP. *PRPF31* is a common causative gene of adRP, after *RHO* and *PRPH2*, with over 40 RP-causing mutations identified to date [48]. Furthermore, *PRPF31* mutations have been reported to cause both RP and MD [1]. According to study on affected family with adRP in a large Chinese family, the age of RP patients ranged from 22 to 71 years, although the onset of night blindness extended from infancy to the fourth year of life [48].

The phenotype of *PRPF31* disease-causing mutations is highly heterogeneous, with extreme inter- and intra-familial variability [17, 34]. Although these mutations cause adRP, they are non-penetrant, and several mutations are present without clinical manifestation [48-50]. As a result, a few carriers of these mutations are blind, whereas others are asymptomatic [51]. Genetic modifiers are a potential cause of phenotypic variability. *CNOT3* encodes a protein of the CCR4-NOT complex, which is a conserved multiprotein structure that regulates gene expression. It is also a modifier in *PRPF31*-associated adRP, which explains the incomplete penetrance observed in families segregating these mutations [17].

In adRP, the prevalence rate of *PRPF31* mutations in different populations varies from 1% to 8% [52]. In the United States, this frequency is approximately 5%. In Europe, the prevalence is higher (6.7%) than in the American population. *PRPF31* mutations have also been

reported in a Swedish population [17]. The prevalence of PRPF31 mutations in the Spanish population is estimated to be 7.6%, which is similar to that found in a French population (6.7%) [53]. However, these mutations are extremely rare in Asian population-based databases [29]. The prevalence of mutations in *PRPF8*, *PRPF31* and *SNRNP200*, is high (19.8%) in the Belgian population. Mutations in *PRPF31* have a prevalence of 10.5% (53% of the 19.8%). Together, mutations in *PRPF8*, *PRPF31*, and *SNRNP200* are the major causative genes of adRP in the Belgian population [24].

In addition, *PRPF3* (RP 18, SNRNP90) contains the three main mutations associated with ethnic variability in RP. The mutation T494M, the most frequent substitution in this gene, is a common causative mutation in adRP. T494M has been detected in American, Danish, English, Spanish, Swiss, Korean, and Japanese adRP families. P493S was identified in sporadic RP cases from Germany or the UK, as well as in a Caucasian adRP family in the USA. A489D has been referred to as an adRP family in Spain. On the other hand, *PRPF3* mutations are rare in Chinese adRP patients [44].

RP1

RP1 is located on 8q12 chromosome and contains four exons. It encodes a 2,156 amino acid protein, oxygen-regulated protein 1 [21, 54, 55]. It is localized at the connecting cilia of rods and cones [55] and contributes to photoreceptor development, organization of photoreceptor OSs, and regulation of photoreceptor microtubules [54, 55]. Disease-causing mutations in this gene may cause both adRP and arRP [1, 3, 15, 24, 56], often associated with a relatively good prognosis [54]. In 1999, it was thought to be an adRP-causing gene, but later arRP cases were associated with RP1 mutations. According to the estimate, disease-causing mutations in this gene account for 5% and 1% of adRP and arRP cases, respectively [55]. In addition to adRP and arRP, some studies have provided evidence that arCRD and arMD are also *RP1*-associated phenotypes [57].

To date, over 150 disease-causing mutations have been detected in RP1, most of which are truncation variants. However, the pathway responsible for the dominant/recessive mutation effect remains unknown. It has been reported that deleterious effects of the truncated RP1 protein, caused by *RP1* nonsense mutations, are mostly implicated in the development of retinal degeneration. In addition, it has been proposed that there are four distinct categories of truncation mutations in *RP1* that affect the progression of RP differently [55].

Incomplete penetrance and variable expressivity have been observed in individuals carrying *RP1* mutations, resulting in phenotypic variability, including the age of onset, abnormalities of the central and mid-peripheral retina, visual acuity and visual fields, and ERG findings. RP patients with homozygous or heterozygous *RP1* mutations may develop arRP, which progresses in childhood, presenting with night blindness and progressive loss of visual acuity until the twentieth year of life. However, *RP1* mutation carriers mostly appear asymptomatic, whereas an increased risk of hypertriglyceridemia has been reported in homozygous carriers of p.N985Y [54].

A nonsense mutation at codon 677 (p.R677) was one of the first analyzed *RP1* mutations, which was estimated to be present in approximately 3% of adRP patients in North America [21]. Disease-causing mutations have also been identified in Iranian [28], Japanese [29] Korean [30], and Spanish families [27] with adRP, whereas disease-causing mutations were also identified in Spanish patients with arRP [55].

CRX

CRX is localized on chromosome 19q13.33. It contains four exons and encodes a protein of 299 amino acids that is a homeodomain transcription factor [2, 6, 58]. *CRX* and *NRL* are photoreceptor cell transcription factors that control the expression of photoreceptor cell-specific genes, and both are known be mutated in the RP. Those mutations may prevent the development of rods and cones, and may cause degeneration of these cells over time [19]. Mutations in *CRX* can also lead to recessive, dominant, and de novo LCA, adCRD [2, 6, 19], and adRP [33, 35, 58]. ArRP-causing mutations in *CRX* have been reported in Japanese and other populations [29]. The phenotype of *CRX* mutations is heterogeneous, and incomplete penetrance of the mutations may be related to the influence of other genes [59, 60].

CRX is also a common CRD-causative gene [32, 33, 60], and missense changes are most frequently found in adRP-associated genes [27]. *CRX* mutations, like *GUCY2D*, *AIPL1*, and *RPGRIP1* mutations result in poor visual acuity, starting within the first year of life [61]. In addition, *CRX* mutations associated with LCA often involve hyperopia [7].

RPE65

RPE65 is *loca*ted on 1p31.2, and encodes a 65-kDa retinol isomerase called RPE-specific protein that contributes to the visual cycle by renewing 11-*cis* retinal from *all-trans* retinol [2, 6, 62]. It is a member of the carotenoid cleavage oxygenase (CCO) enzyme family [61, 63, 64].

More than 100 mutations in *RPE65* have been associated with arLCA [2, 6, 35, 62, 65, 66], RP [6, 35, 62, 65], and CRD

[67]. Additionally, a potential association with AVMD has been described [64]. More specifically, *RPE65* mutations can cause both adRP and arRP [1, 6], but most mutations are associated with arRP [62].

RPE65-associated adRP also affects the choroid [63]. *RPE65* mutations cause severe retinal dystrophies, mainly due to protein dysfunction and recessive inheritance. The c.1430A>G:p.Asp477Gly (D477G) mutation is the only known exception to this rule to date, as it is the cause of delayed-onset adRP and also affects the choroid and the macula [62]. Various phenotypes are present in D477G mutation carriers, including differences in the age of disease onset and disease severity, while most of them initially present with central visual impairment. They differ from typical RP patients, who present with progressive visual field loss starting from the mid-region and progressing to the far periphery [63, 64].

Patients with disease-causing mutations in *RPE65* present early-onset degeneration, keratoconus, nystagmus, white dot deposits, and clumped pigment in advanced disease [68]. Severe visual impairment and night blindness are observed during infancy, and photophobia is observed during childhood [69]. High hyperopia is an additional common feature [67]. *RPE65* mutations are also responsible for progressive visual impairment in older individuals. In addition, the appearance of symptomatology after infancy has been associated with better prognosis [61].

The highest prevalence of *RPE65* variants is encountered in Caucasian populations, while high frequencies (16.5%) of *RPE65* variants have been reported in the Indian population [70]. *RPE65* mutations are responsible for approximately 16% of LCA cases, although it seems that this gene is not involved in Chinese LCA cases [67, 71]. On the other hand, adRP cases caused by *RPE65* have been identified among Irish families, and is thought to reflect an Irish founder mutation [62, 64].

ABCA4

ABCA4 consists of 50 exons and is located on chromosome 1p13 [72]. The encoded protein is an ATP-binding cassette (ABC) transporter protein localized to the rims of rod and cone discs [6, 72-75]. The main function of the ABCA4 protein is to transfer both N-retinylidene-phosphatidylethanolamine and phosphatidylethanolamine from OS disc membranes of photoreceptors to the cytoplasmic leaflet during phototransduction. Thus, ABCA4 eliminates potentially toxic retinoid compounds from photoreceptors [72, 74, 75].

At present, more than 800 mutations have been linked to *ABCA4*-associated phenotypes. *ABCA4* mutations may be simple single-base substitutions or may be as extensive as the deletion of a few exons. However, most are missense mutations [72]. The severity of the retinal dystrophy phenotype may be related to the degree of mutation pathogenicity, which depends on their localization in various regulatory regions of the gene and the effect of the mutation on the amino acid composition of the protein molecule [76].

ABCA4 mutations are heterogeneous and are the most common cause of central retinal dystrophies [30, 33]. They can cause autosomal recessive Stargardt disease (arSTGD1), CD, CRD, and arRP [75-79]. In fact, *ABCA4* is the major causative gene of STGD [36], and are commonly responsible for arCRD. *ABCA4* has been reported as a major contributing gene to arCRD, whereas other known arCRD-related genes, including *PROM1*, accounts for only a minor fraction of the reported cases [80].

Some studies have also indicated that *ABCA4* mutations are associated with atypical Usher syndrome [3, 81]. The most severe arRP phenotype involves injury to both the rods and cones. To date, 27 missense/nonsense mutations, nine splicing mutations, four deletions, and a complex rearrangement are thought to be responsible for homozygous or compound heterozygous arRP [82].

Additionally, disease-causing mutations in *ABCA4* are extremely heterogeneous with respect to ethnicity. In European patients, the p.G1961E mutation is prevalent at a frequency of 20.5%. On the other hand, p.A1773V and p.G818E are present in 17% and 15% of Mexican patients, respectively [77]. Among Thai patients, *ABCA4* mutations are mainly responsible for the RP phenotype [6], whereas they are very rare in Chinese and Polish patients with arCRD [73, 83]. However, their frequency ranges from 16.13% to 65% in European and American patients [73].

Electrophysiology contributes significantly to the diagnosis and follow-up of *ABCA4*-associated retinal disorders. Different phenotypeswere identified using different ERG patterns. In STGD, multifocal ERG (mERG) is typically attenuated with ffERG remaining normal or slightly affected. In CRD, mERG is always significantly attenuated, as are the cone responses in ffERG. ArRP is associated with an initial attenuation of the ffERG rod response, followed by reduced cone responses [84, 85].

CRB1

C*RB1* encodes two proteins (1,376 and 1,406 amino acids long). It contains 12 exons and 11 introns and is located on 1q31.3 [6, 86], The CRB1 protein is an extracellular signal protein. CRB1 includes three laminin A globular (AG)-like, a C-type lectin (CTL), and 19 epidermal growth factor (EGF)-like domains, and is extremely important for the formation and function of the retina [40, 86-88].

To date, more than 200 *CRB1* mutations implicated in arRP pathogenesis have been identified [40]. Among patients with RP attributable to *CRB1* mutations, severe forms of retinal degeneration, such as LCA, appear in patients with null mutations in both alleles, including nonsense and frameshift mutations, whereas less aggressive forms, such as RP, are produced by heterozygous missense mutations [88, 89]. *CRB1* mutations that lead to RP are associated with night blindness, followed by progressive peripheral vision loss, rod and cone degeneration, and rarely associated with complete blindness [88]. Disease-causing mutations in *CRB1* frequently cause hyperopia [7]. *CRB1* mutations are related to various phenotypes and retinal dystrophies, such as early-onset RP, LCA, and CRD, and central phenotypes, including MD and foveal retinoschisis [6, 33, 35, 40, 61, 82, 86, 88, 90-92].

In addition, *CRB1* mutations are responsible for 3–9% of non-syndromic arRP cases [91]. Moreover, it was observed that 9–15% of LCA cases have mutations in *CRB1* [93]. Recessive *CRB1* mutations may also cause CRD with MD in childhood, with electronegative ERG [94]. These mutations are also responsible for adSTGD1-like phenotypes [36]. The variability of clinical manifestations in arRP patients with the same mutation in *CRB1* indicates that other unknown factors may affect the pathogenesis [95].

CRB1 mutations frequently cause autosomal recessive retinal degeneration of early-onset in individuals from Israel, Palestine, and Spain [40, 89]. *CRB1* mutations have been reported in four Chinese families. *CRB1* sporadic mutations have been reported in RP subjects at a frequency of 5.8% [40, 92]. The most common types of arRP-causing mutations in patients from Israel and Palestine are also localized in *CRB1*. Furthermore, they are also present in Thai families with non-syndromic RP [96]. *CRB1* mutations are also the most frequent cause of LCA among German patients [97]. Moreover, the prevalence of *CRB1* mutations in a Danish LCA cohort was estimated at 7% [70]. *CRB1* mutations have also been reported in the Brazilian CRD population [86]. In addition, it has been reported that Tunisian families with RP present mutations in *CRB1*, which are characterized by preserved para-arteriolar RPE [68].

PROM1

PROM1 is located at 4p15.32 [6, 39, 98] and consists of 27 exons. It encodes prominin-1, a five-transmembrane-domain glycoprotein [6, 39, 84, 98]. The gene contributes to the development of disk membranes and is localized at the OS base of rods and cones. Stem and progenitor cells of several systems, such as neural and hematopoietic cells, or epithelial, glial, and photoreceptor cells of various organs, express the protein [98].

Thirty-five *PROM1* mutations have been identified [39]. The different disease-causing mutations in *PROM1* have been suggested to be related to a variety of retinal degenerative phenotypes, such as arRP with MD, adSTGD1-like MD, autosomal dominant bull's-eye MD, and CRD [1, 84, 99]. It has been reported that each *PROM1* mutation is related to a different phenotype. Missense mutations are mostly related to adSTGD1-like or bull's-eye MD. On the other hand, diseases such as RP and severe CRD with MD and nyctalopia are caused by nonsense and frameshift mutations in this gene [39, 83, 100].

Moreover, *PROM1* mutations are strongly related to adCRD or arCRD [30, 32, 33, 80, 98] and adSTGD1-like phenotypes [30, 34, 84, 101, 102] In addition, carriers of *PROM1* mutations have clinical manifestations of adMD [99]. *PROM1* mutations are associated with high myopia [100], while the first symptoms of RP patients with *PROM1* mutations are nyctalopia and loss of visual fields [98].

In Thai and Chinese families, mutations in *PROM1* are often responsible for arRP [39, 96]. In addition, recessive *PROM1* mutations have been implicated in a Spanish family presenting with severe RP accompanied by MD and myopia. In these cases, PROM1 dysfunction may cause retinal degeneration [100].

PDE6

Mutations in the gene encoding cyclic guanosine monophosphate (cGMP) phosphodiesterase 6 (*PDE6*) are responsible for approximately 8% of arRP cases. Abnormal cGMP metabolism may affect the visual signaling pathway, resulting in the death of photoreceptors and retinal degeneration. Hence, the regulation of cGMP concentrations in rods and cones is thought to be vital. Dysfunction of PDE6 may lead to photoreceptor degeneration, although the mechanisms initiating rod photoreceptor death are unclear [14].

The *PDE6* complex (including its PDE6A, PDE6B, PDE6G subunits) is crucial for rod phototransduction. Little is known about the processes that induce rod photoreceptor death in RP; however, low PDE6 activity apparently results in rod–cone devolution. All PDE6 subunits are necessary for proper photoreceptor function. *PDE6A* and *PDE6B* mutations seem to, quite commonly, induce arRP and heterozygous carriers of mutations in *PDE6* are thought to be at a significant risk of visual loss. In contrast, *PDE6G* mutations are likely to cause early-onset arRP [14].

In particular, the *PDE6B*, located on 4p16.3, encodes the rod cGMP phosphodiesterase beta subunit. *PDE6B* mutations are related to arRP [6, 103, 104], and they have

been identified in specific ethnic groups [30, 68, 105]. In the Korean population and in Caucasian Jews, *PDE6B* mutations are an extremely common cause of arRP [30, 105]. RP caused by *PDE6B* mutations is characterized by childhood onset, night blindness, and photophobia [79, 103], Mutations in *PDE6B* are also responsible for adCSNB [6].

TULP1

TULP1, located on 6p21.31, is expressed only by rods and cones, and encodes the 542-amino acid tubby-like protein 1, a member of the homonymous protein family [6, 106, 107]. It consists of 15 exons in a 15-kb region. Rhodopsin, which is synthesized in the ISs of rods, is transported by TULP1 to the OSs via the connecting cilium (CC) [107, 108]. *TULP1* is one of nine genes that have been implicated in the pathogenesis of both RP and LCA (*RPE65, CRB1, SPATA7, CRX, RDH12, LRAT, TULP1, IMPDH1,* and *PRPH2*) [35]. Disease-causing mutations in *TULP1* have been reported in juvenile-onset arRP, rod–cone dystrophy (RCD), and arLCA, implicating this gene with retinal degeneration [6, 15, 35, 61, 106-108]. Mutations in this gene have also been reported in Thai families with arRP and arLCA [96].

There is clinical and genetic overlap between (early-onset) arRP and LCA, and it is often very difficult to differentiate these two conditions [107]. Biallelic *TULP1* variants are associated with nystagmus, progressive nyctalopia, myopia, abnormal ERG, normal visual acuity and visual field in the first decade of life, and abnormalities of the peripheral retina [106, 108, 109]. In particular, nystagmus appears to be an unstable clinical feature [109].

C8orf37

C8orf37, a gene located on 8q22.1 [6], encodes a 207-amino acid protein of approximately 23 kDa whose function has not been determined. The C8orf37 protein colocalizes with γ-tubulin in immunolocalization studies of the retina, which is a basal body marker at the CC of rods and cones [41]. Therefore, mutations in *C8orf37* may hinder intracellular traffic and thus play a role in the pathophysiology of RP, CRD, and BBS [1, 15, 110].

C8orf37 mutations cause arRP and arCRD [6, 15, 110, 111]. However, *C8orf37* mutations are implicated in the pathogenesis of some BBS (BBS21) cases [110]. The relationship between *C8orf37* mutations and BBS (BBS21) suggests that *C8orf37* mutation carriers should be under surveillance to prevent the potential development of BBS-contributing morbidities, such as obesity, renal abnormalities, diabetes, and hypertension [110, 111].

The phenotypic heterogeneity associated with *C8orf37* mutations is wide, and overlap between RP and CRD is common. Distinguishing between RP (nyctalopia and developing visual field constriction) and CRD (photophobia, loss of central vision) greatly depends on their early symptoms. Given the substantial phenotypic overlap at the early stages, it is difficult to make a differential diagnosis of these conditions in their most severe presentations [41].

C8orf37 is also reported to be a causative gene of arRP in Thai families [96]. In addition, *C8orf37* mutations have been reported to cause RP in two families from Pakistan. However, they are thought to be a rare cause of retinal dystrophy in this population [41].

RPGR

RPGR, located on Xp11.4 [6, 112], *RP2*, and *OFD1* are genes associated with xlRP [10, 113]. Mutations in *RPGR* are responsible for approximately 70–90% of xlRP cases and mutations in *RP2* cause around 6–20% of xlRP cases [10, 114]. There are more than 10 alternatively spliced transcripts *of RPGR*, while *RPGRconst* and *RPGR*^{ORF15} are the two major RPGR isoforms identified [10, 114]. The phenotypic spectrum of *RPGR* mutations is highly heterogeneous [42]. Mutations in *RPGR*^{ORF15} may provoke xlRP, X-linked MD (xlMD), X-linked CD (xlCD), and X-linked atrophic MD [6, 10, 33, 73, 112, 114]. Approximately 50–60% of *RPGR* mutations are clustered in the ORF15 exon, indicating that it is a hotspot for mutations. Most of these mutations are frameshift mutations, because the purine-rich structure of the ORF15 exon apparently promotes polymerase arrest and slipped-strand mispairing events. Truncated products of RPGR^{ORF15} of different lengths, affecting RPGR^{ORF15} glutamylation, are caused by frameshift mutations [10, 114]. In addition, impaired glutamylation of RPGR^{ORF15} is triggered by *TTLL5* disease mutations, causing retinal dystrophy. Hence, in the absence of RPGR^{ORF15} glutamylation, patients with *TTLL5* mutations present with retinal pathology because these two genes are components of a common disease pathway [18].

A large deletion in *RP2* and four frameshift *RPGR* mutations have been identified in five families from China affected by xlRP [10]. Mutations in these genes have also been detected in Jordanian families with this disease [113]. Furthermore, disease-causing mutations have been identified in Japanese and other populations [29].

Mutations in *RPGR* cause LCA and juvenile RP. However, cases have been reported where the disease course was benign, with good visual acuity at presentation, which remained fairly stable up to over 40 years of age [34].

Nyctalopia and vision decline are present in RP-affected males with *RP2* mutations. Males present with a graver phenotype than carrier females, who show different degrees of severity of myopia. With *RP3* mutations, males

present with more severe phenotypes, while carrier females have several different clinical manifestations, from asymptomatic to severe RP. In addition, most of the females present with reduced vision, but rarely progress to complete blindness [112].

The genotypic spectrum of *RPGR* variants has also been associated with systemic manifestations. The identification of these features in males and the phenotype in carrier females allows confirmation of pathogenic variants [115]. In addition, blindness by the age of 40 years occurs in approximately 20% and 55% of RP and CD/CRD patients, respectively [116].

USH2A

USH2A is located on chromosome 1q41 [6]. It consists of 72 exons and encodes usherin, a 5,202 amino acid protein. This protein is localized at the apical IS recess of rods and cones of mammals, corresponding to the periciliary ridge complex that appears in the rods and cones of amphibia [117].

It is estimated that 10–15% of arRP cases and 30–40% of Usher syndrome type 2 cases are associated with *USH2A* mutations [117]. Moreover, mutations in *USH2A*, *RPGR*, *PRPF31*, and *EYS* are implicated in 48% of RP cases with known mutations [34]. Because *USH2A* mutations may be responsible for non-syndromic RP and Usher syndrome, their presence in a family necessitates a hearing examination for these patients [3]. In addition, late-onset non-syndromic arRP may be associated with *USH2A* mutations [79].

Approximately 7% of RP cases in the USA are associated with mutations in *USH2A*. In addition, *USHA2* mutations causing arRP have a high prevalence and show phenotypic variations among Spanish RP patients [117]. Approximately 74–90% of Usher syndrome 2 cases in Caucasians are related to *USH2A*, which is also thought to be a significant causative arRP gene. Among Japanese patients with arRP, the prevalence of these mutations is 4%. However, the Japanese and Caucasian population profiles of these mutations differ [118]. In addition, *EYS* and *USH2A* are thought to be the major genes responsible for RP in Japan [29, 119]. Furthermore, there are specific *USH2A* mutations associated with RP, without hearing, loss among Chinese and Thai patients [96, 120]. Finally, *USH2A* seems to be important in the pathogenesis of the disease among Israeli IRD cohorts [81] and arRP Korean families [30].

RDH12

RDH12 is located on 14q24.1, and encodes an NADPH-dependent retinal reductase that is a member of the retinol dehydrogenase family. *RDH12* plays a vital role in the conversion of all-*trans* retinal and 11-*cis* retinal to their respective retinols. The protein is expressed in the ISs of rods and cones and plays a vital role in the cyclic regeneration of the 11-cis retinal and cone opsins [2, 6, 61].

RDH12 mutations, which account for 3–7% of all ar retinal dystrophy cases, are significant causative genes of LCA [2, 6, 35, 61, 65, 90]. Over 60 *RDH12* mutations have been reported, mainly in patients with LCA and in early-onset retinal dystrophy cases occurring in families with arRP. Based on this, *RDH12* mutations may cause many severe forms of blindness [61].

RP *RDH12* mutations are commonly associated with juvenile RP [68]. Late-onset and mild adRP may be caused by heterozygous *RDH12* mutations [61, 99]. Retina-wide disease, of early-onset, accompanied by abnormalities particularly in the central retina, may be caused by *RDH12* mutations. This disease, with less rod dysfunction, has many similarities to early-onset CRD [121].

BEST1

BEST1, which is localized on 11q12-13, consists of 11 exons and encodes a protein named bestrophin-1 [2, 122]. It is expressed predominantly in RPE and is a Ca^{2+}-activated Cl^- channel. It is an inhibitor of the intracellular voltage-dependent Ca^{2+} channel and HCO_3^- transporter [122, 123].

More than 300 *BEST1* mutations have been identified. They cause bestrophinopathies, such as BEST vitelliform MD (BVMD) and autosomal recessive bestrophinopathy (arB). Patients with BVMD and arBs present with wide genetic and phenotypic variability [123].

Furthermore, *BEST1* mutations are associated with adRP and arRP [1, 124], LCA [123], AVMD, and adSTGD1-like phenotypes [36]. *BEST1* is considered to be the major causative gene of vitelliform MD (VMD), even though many of these patients have mutations in genes such as *IMPG1/IMPG2*, but not in *BEST1* or *PRPH2* [37].

SPATA7

SPATA7 is localized on chromosome 14q313 and encodes a spermatogenesis-associated protein 7 [6]. The SPATA7 protein, as a ciliary protein, is located at the primary cilium of cells and at the CC of rods and cones [125].

Mutations in *SPATA7* lead to both arRP and arLCA [6, 35, 90]. Furthermore, SPATA7 binds to the RP GTPase regulator interacting protein 1 (RPGRIP1), a CC protein that is related to LCA. The apoptosis of rods, which is caused by protein mislocalization, is probably implicated in the development of LCA and juvenile RP [125].

Patients with *SPATA7* mutations show disc pallor, arteriolar thinning, and RPE mottling [90]. There are indications that *SPATA7* mutations account for a

significant number of LCA cases in the Chinese population (4.6% of LCA patients) [125].

NR2E3

NR2E3, located on 15q23, encodes the nuclear receptor subfamily 2 group E3 [2]. Two domains are included in NR2E3, the DNA-binding domain (DBD) and the ligand-binding domain (LBD), at the N- and C-terminus end, respectively. These domains are the *NR2E3* regions most commonly mutated [126].

Mutations in *NR2E3* are responsible for arRP and dominant and recessive retinopathy. Other diseases, including recessive Goldmann–Favre syndrome and recessive enhanced S-cone syndrome (ESC), may also be caused [2, 19]. Mutations in this gene can also lead to adRP [1]. Diagnosis is complicated by the presentation of various clinical manifestations and the severity of retinal degeneration caused by these mutations. Patients with *NR2E3* mutations may present with Goldmann-Favre syndrome (GFS) features, typical ERG pattern of ESCs, or clumped pigmentary retinal degeneration [126]. In addition, RP disease-causing mutations in *NR2E3* are frequently associated with hyperopia [7].

Significant pathogenic mutations have been reported in various populations, including Thai patients [96], Tunisian families [68], and Indian arRP cases [109].

TTC8

TTC8, located on 14q32.11, encodes tetratricopeptide-repeat-domain 8 and is associated with arRP and recessive BBS [6]. A premature stop codon located in exon 6 of the gene may be triggered by a frameshift mutation in the previous exon. The frameshift mutation in exon 5 also results in the production of *TTC8* that lacks the normal tetratricopeptide-repeats 11 and 15. Nonsense and frameshift mutations may reduce translation of the encoded protein. As a result, compound heterozygous patients lack a functional TTC8 protein, a condition that results in the development of BBS type 8. *TTC8* mutations are found in only 2.8% of all patients with BSS. More specifically, in Japan, one family each with *BBS2*, *BBS5*, and *BBS7* homozygotes have been reported, along with a family with *BBS10* compound heterozygotes. However, BBS patients with *TTC8* mutations are extremely rare [127].

CEP290

Heterozygous *CEP290* mutations are associated with LCA, early-onset RP [89], and syndromic RP, as it is associated with BBS type 14 [14]. Mutations in this gene are responsible for LCA. The protein is localized in the CC of rods and cones and in the centromeres of diving cells. *CEP290* mutations may cause a reduction in OS length and thickness of several retinal layers. Poor visual acuity and rod–cone vision loss were observed in these patients [128]. Sequence analysis in a Danish LCA cohort indicated that *CEP290* mutations were responsible for approximately 7% of the cases [70].

CERKL

CERKL, located on 2q31.3 [6], encodes a ceramide-kinase-like protein and is associated with arRP [3, 79] and CRD. Mutations in the gene may provoke bone-spicule pigmentation with white dots, RPE atrophy in the macular area, chorioretinal atrophy in the central retina, and decreased visual acuity [79].

CNGA3

CNGA3 encodes the functional components of the phototransduction cascade in cone photoreceptors [129]. Several *CNGA3* mutations have been implicated in the pathogenesis of various diseases, including IRDs, and more specifically with autosomal recessive achromatopsia, complete or incomplete achromatopsia, CD or CRD, LCA, and RP [66, 130-133]. *CNGA3* mutations have been identified in the Korean population [30] and in Israeli families [81] as a significant cause of IRDs. In addition, mutations in this gene seem to be significant among Chinese patients with CRD and achromatopsia. Hence, many cases of severe retinal dystrophies of early-onset may be related to *CNGA3* mutations [134].

SLC7A14

Disease-causing mutations in the *SLC7A14* cationic transporter gene are responsible for arRP and LCA [135]. *SLC7A14* is thought to be an important causative gene for RP in Japanese patients with arRP or sporadic RP. The frequency and pathogenicity of *SLC7A14* mutations may differ in terms of ethnicity, and these mutations were unlikely in Japanese patients [136].

MERTK

MERTK, a member of the MER/AXL/TYRO3 receptor kinase family, is composed of 19 exons [137] and encodes a 999 amino acid transmembrane protein [66, 137]. Several cells and tissues express this protein, including macrophages, RPE, prostate, lung, and kidney [137].

Approximately 1% of autosomal recessive retinal dystrophy cases are associated with mutations in *MERTK*. Progressive retinal dystrophies with childhood onset and macular defects characterize these patients [137]. *MERTK* mutations cause approximately 2% of severe IRD cases, including RP and CRD [138]. All known mutations are *loss-of-function* mutations [139]. Patients present with increased sensitivity to light and with dark adaptation problems [33]. Germline *MERTK* mutations related to arRP have been identified in the Chinese population [139].

IMPDH1

Inosine monophosphate dehydrogenase 1 is the protein product of *IMPDH1*, which is located on 7q32.1 [2, 6]. This protein is involved in purine or amino acid synthesis [2]. Disease-causing mutations in *IMPDH1* lead to adLCA and adRP [2, 6, 7, 35].

SEMA4A

SEMA4A, located on 1q22 chromosome, encodes semaphorin 4A and is associated with adRP and adCRD [2, 6]. *SEMA4A* mutations are one of the most common causes of CRD [32].

LRAT

LRAT, located on 4q32.1 chromosome, encodes lecithin retinol acyltransferase, and mutations in this gene are responsible for both arRP and arLCA [6, 35]. In specific populations, such as the Danish population, *LRAT* is a significant causative gene of LCA [70]. Disease-causing mutations in *LRAT* frequently also cause hyperopia in RP patients [7]. Table 5 summarizes the overlap between genes causing RP and causing other IRDs, and Table 6 summarizes all abbreviations used in the text.

This review, in addition to its strengths, has several limitations. The present review focused on articles published in the last decade by using two of the known databases, PubMed and Google Scholar; however, other databases were not searched. It also focused most on important genes that are implicated in RP pathogenesis, while other rare pathogenic mutations in less significant genes were not included. The review is concisely referred to some types of management that may be developed and used in the future, including antioxidant ingredients, stem cells, and gene therapy, without emphasis. Future research should focus on the individual types of RP, and particularly the progression and clinical manifestations caused by specific variants in order to identify more pathogenic mutations from other less aggressive mutations. This may enhance the effort to achieve specialized management, such as promising gene therapy, for each disease-causing mutation.

Table 3. Genes reported to cause autosomal dominant retinitis pigmentosa.

GENE	CHROMOSOME	OTHER DISEASES
***BEST1* (Bestrophin 1)**	11q12.3	Dominant Vitreoretinochoroidopathy [12, 32], Recessive Bestrophinopathy [12, 118, 119], Recessive RP [12, 18], Dominant MD [32], Best type [12, 119]
***CRX* (Cone-Rod Homeobox)**	19q13.32	Recessive, Dominant and de novo LCA [2, 6], Dominant CRD [12, 18, 29]
***GUCA1B* (Guanylate Cyclase Activator 1B)**	6p21.1	Dominant MD [12, 18]
***IMPDH1* (Inosine Monophosphate Dehydrogenase 1)**	7q32.1	Dominant LCA [2, 6, 12, 18]
***KLHL7* (Kelch Like Family Member 7)**	7p15.3	[12, 18]
***NRL* (Neural Retina Leucine Zipper)**	14q11.2	Recessive RP [12, 18]
***NR2E3* (Nuclear Receptor Subfamily 2 Group E Member 3)**	15q23	Recessive RP [12, 18], Recessive Goldmann–Favre Syndrome [12, 17, 18], Recessive ESC [2, 12, 17, 18]
***PRPF3* (Pre-MRNA Processing Factor 3)**	1q21.2	[12, 18]
***PRPF6* (Pre-MRNA Processing Factor 6)**	20q13.33	[18]
***PRPF8* (Pre-MRNA Processing Factor 8)**	17p13.3	[12, 18]
***PRPF31* (Pre-MRNA Processing Factor 31)**	19q13.42	[12, 18]
***PRPH2* (Peripherin 2)**	6p21.1	Dominant AVMD [1, 6], Dominant CRD [6, 12, 18], Dominant Central Areolar Choroidal Dystrophy [1, 6, 12]
***RDH12* (Retinol Dehydrogenase 12)**	14q24.1	Recessive LCA [2, 6, 12, 18]
***RHO* (Rhodopsin)**	3q22.1	Dominant CSNB [2, 6], Recessive RP [2, 6, 12, 18]
***RP1* (RP1 Axonemal Microtubule Associated)**	8q12.1	Recessive RP [12, 18]
***RP9* (RP9 Pre-MRNA Splicing Factor)**	7p14.3	[12, 18]
***RPE65* (Retinoid Isomerohydrolase RPE65)**	1p31.2	Recessive RP [12, 18], Recessive LCA [2, 6, 18]
***SEMA4A* (Semaphorin 4A)**	1q22	Dominant CRD [2, 6, 12, 18]
***SNRNP200* (Small Nuclear Ribonucleoprotein U5 Subunit 200)**	2q11.2	[12, 18]
***TOPORS* (TOP1 Binding Arginine/Serine Rich Protein, E3 Ubiquitin Ligase)**	9p21.1	[12, 18]

Abbreviations: RP, Retinitis Pigmentosa; MD, Macular Dystrophy; LCA, Leber Congenital Amaurosis; CRD, Cone–rod Dystrophy; ESC, Enhanced S-cone Syndrome; AVMD, Adult Vitelliform Macular Dystrophy; CSNB, Congenital Stationary Night Blindness.

Table 4. Genes reported to cause autosomal recessive retinitis pigmentosa.

GENES	CHROMOSOME	OTHER DISEASES
ABCA4 **(ATP Binding Cassette Subfamily A Member 4)**	1p22.1	Recessive MD [12], Recessive CRD [12, 13], Autosomal Recessive Stargardt Disease [12, 13, 71]
BEST1 **(Bestrophin 1)**	11q12.3	Dominant Vitreoretinochoroidopathy [12, 32], Recessive Bestrophinopathy [12, 119], Recessive RP [12], Dominant MD [12, 13], Best type [12, 13, 32, 119]
C8ORF37 **(Chromosome 8 Open Reading Frame 37)**	8q22.1	CRD [6, 13, 14]
CERKL **(Ceramide Kinase Like)**	2q31.3	CRD [12, 13, 75]
CNGA3 **(Cyclic Nucleotide Gated Channel Subunit Alpha 3)**	2q11.2	CRD [12, 62] and Achromatopsia [12, 126]
CRB1 **(Crumbs Cell Polarity Complex Component 1)**	1q31.3	Recessive LCA [12, 13] and CRD [12, 13, 89]
EYS **(Eyes Shut Homolog)**	6q12	[12, 13]
IMPG2 **(Interphotoreceptor Matrix Proteoglycan 2)**		[12, 13]
LRAT **(Lecithin Retinol Acyltransferase)**	4q32.1	Recessive LCA [6, 12, 13, 31]
MERTK **(MER Proto-Oncogene, Tyrosine Kinase)**		CRD [12, 13, 134]
NR2E3 **(Nuclear Receptor Subfamily 2 Group E Member 3)**	15q23	Dominant RP [2, 12, 13], Recessive ESC [2, 12, 13, 17]
NRL **(Neural Retina Leucine Zipper)**	14q11.2	Dominant RP [12, 13]
PDE6A **(Phosphodiesterase 6A)**		[12, 13]
PDE6B **(Phosphodiesterase 6B)**	4p16.3	Dominant CSNB [6, 12, 13]
PDE6G **(Phosphodiesterase 6G)**		[12, 13]
PROM1 **(Prominin 1)**	4p15.32	Recessive RP with Macular Degeneration [13], Autosomal Dominant and Recessive CRD [13, 26], STGD [13, 26, 28]
RDH12 **(Retinol Dehydrogenase 12)**	14q24.1	Autosomal Recessive LCA [2, 6, 13]
RHO **(Rhodopsin)**	3q22.1	Dominant CSNB [2, 6, 11], Recessive RP [2, 12, 13]
RP1 **(RP1 Axonemal Microtubule Associated)**	8q12.1	Dominant RP [12, 13]
RPE65 **(Retinoid Isomerohydrolase RPE65)**	1p31.2	Recessive LCA [6, 12], Autosomal Dominant RP [12, 13] and CRD [2, 12, 63]
SLC7A14 **(Solute Carrier Family 7 Member 14)**	3q26.2	LCA [13, 131]
SPATA7 **(Spermatogenesis Associated 7)**	14q313	Autosomal Recessive LCA [6, 12, 13, 31]
TTC8 **(Tetratricopeptide Repeat Domain 8)**	14q32.11	Recessive BBS [6, 12, 13]
TULP1 **(TUB Like Protein 1)**	6q21.31	Recessive LCA [6, 12, 13, 31]
USH2A **(Usherin)**	1q41	Recessive Usher Syndrome [12, 13, 113]

Abbreviations: MD, Macular Dystrophy; CRD, Cone–Rod Dystrophy; RP, Retinitis Pigmentosa; LCA, Leber Congetinal Amaurosis; ESC, Enhanced S-cone Syndrome; CSNB, Congenital Stationary Night Blindness; BBS, Bardet–Biedl syndrome.

Table 5: Overlap between genes causing retinitis pigmentosa and those causing other inherited retinal diseases.

RP-causing Genes → Overlapping Disease ↓	*ABCA4*	*BEST1*	*C8orf37*	*CERKL*	*CNGA3*	*CRB1*	*CRX*	*IMPDH1*	*LRAT*	*PDE6*	*PROM1*	*PRPH2*	*RHO*	*RDH12*	*RP1*	*RPE65*	*RPGR*	*SEMA4*	*SLC7A14*	*SPATA7*	*TULP1*	*USH2A*
CSNB [2, 6]										X			X									
AVMD [2, 36-38, 64]		X										X				X						
Achromatopsia [66, 130-133]					X												X					
LCA [2, 6, 19, 34, 35, 61, 65, 66, 90, 93, 135]						X	X	X	X					X		X	X		X	X	X	
Stargardt Disease [1, 6, 36, 63, 64, 75-79, 84, 99, 130]	X	X			X	X					X	X				X						X
CRD [1, 2, 6, 15, 19, 27, 32-35, 41, 57, 66, 67, 75-79, 84, 99, 116, 117, 121, 130]	X		X	X	X	X	X				X	X		X	X	X	X	X			X	X

Abbreviations: AVMD, Adult Vitelliform Macular Dystrophy; CSNB, Congenital Stationary Night Blindness; LCA, Leber Congenital Amaurosis; CRD, Cone-Rod Dystrophy; ABCA4, ATP Binding Cassette Subfamily A Member 4; BEST1, Bestrophin 1; C8orf37, Chromosome 8 Open Reading Frame 37; CERKL, Ceramide Kinase Like; CNGA3, Cyclic Nucleotide Gated Channel Subunit Alpha 3; CRB1, Crumbs Cell Polarity Complex Component 1; CRX, Cone-Rod Homeobox; IMPDH1, Inosine Monophosphate Dehydrogenase 1; LRAT, Lecithin Retinol Acyltransferase; PDE6, Phosphodiesterase 6; PROM1, Prominin 1; PRPH2, Peripherin 2; RHO, Rhodopsin; RDH12, Retinol Dehydrogenase 12; RP1, RP1 Axonemal Microtubule Associated; RPE65, Retinoid Isomerohydrolase RPE65; RPGR, Retinitis Pigmentosa GTPase Regulator; SEMA4, Semaphorin 4A; SLC7A14, Solute Carrier Family 7 Member 14; SPATA7, Spermatogenesis Associated 7; TULP1, TUB Like Protein 1; USH2A, Usherin.

Table 6. Abbreviations used in the text

Abbreviation	Full description
AVMD	Adult onset Vitelliform Macular Dystrophy
ABC	ATP-Binding Cassette transporter protein
adRP	autosomal dominant RP
adSTGD1	autosomal dominant STGD1-like
arB	autosomal recessive bestrophinopathy
arRP	autosomal recessive RP
arSTGD1	autosomal recessive Stargardt Disease
BBS	Bardet-Biedl Syndrome
BVMD	Best Vitelliform Macular Dystrophy
CTL	C-Type Lectin
CCO	Carotenoid Cleavage Oxygenase
CD	Cone Dystrophy
CRD	Cone-Rod Dystrophy
CSNB	Congenital Stationary Night Blindness
CC	Connecting Cilium
CRB1	CRumBs Homologue 1
cGMP	Cyclic Guanosine MonoPhosphate
CME	Cystoid Macular Edema
DBD	DNA-Binding Domain
ERG	ElectroRetinoGram
ESC	Enhanced S-Cone syndrome
EGF	Epidermal Growth Factor
ffERG	Full-Field ERG
GPCR	G Protein Coupled Receptors
iPSCs	Induced Pluripotent Stem Cells
IRDs	Inherited Retinal Diseases
IS	Inner Segment
LCA	Leber Congenital Amaurosis
LBD	Ligand-Binding Domain
MD	Macular Dystrophies
mERG	Multifocal ERG
NRPE	N-Retinylidene-PhosphatidylEthanolamine
NGS	Next-Generation Sequencing
OCT	Optical Coherence Tomography
OSs	Outer Segments
PRPH2	*Peripherin 2*
PE	PhosphatidylEthanolamine
PDE6	PhosphoDiEsterase 6
PRPF31	PRe-mRNA Processing Factor 31
PROM-1	PROMinin like-1
RPE	Retinal Pigment Epithelium
RP	Retinitis Pigmentosa
RP1	Retinitis Pigmentosa 1
RP2	Retinitis Pigmentosa 2
RP4	Retinitis Pigmentosa 4
RPGR	Retinitis Pigmentosa GTPase Regulator
RPGRIP1	Retinitis Pigmentosa GTPase Regulator Interacting Protein 1
RHO	RHodOpsin
RCD	Rod-Cone Dystrophy
snRNP	Small Nuclear RiboNucleoProtein
TULP1	TUbby-Like Protein 1
USH2	USHer Syndrome Type 2
VMD	Vitelliform Macular Dystrophy
XLCD	X-Linked Cone Dystrophy
XLMD	X-Linked Macular Dystrophy
xlRP	X-Linked RP

CONCLUSIONS

RP is a genetically complicated and heterogeneous disease. To date, approximately 80 genes have been implicated in non-syndromic RP and 30 genes in syndromic RP. The extreme heterogeneity that characterizes RP has led to many attempts to map and analyze the genes that contribute to the appearance and progression of several RP forms, a demanding task as these genes belong to several groups (i.e., genes that encode proteins of the visual cascade, genes encoding proteins of the visual cycle, mitochondrial genes, etc.). To date, approximately 27 adRP, 55 arRP, and 6 xlRP genes have been reported to be pathogenic according to the RetNet and Genecards databases, whereas several genes may be implicated in different patterns of RP inheritance. *RHO* is the gene most often associated with adRP, *USH2A* with arRP, and *RPGR* with xlRP.

Specific genotyping microarrays, gene-by-gene analysis by Sanger sequencing, linkage mapping, NGS, and deletion detection are mainly used for the genetic diagnosis of IRDs, including RP. The main long-term objective of research on mutations associated with RP pathogenesis is the adoption of wide genetic testing. This may provide appropriate information for clinical care and counseling of patients with RP. The expectation is that the eventual verification of disease pathology will offer novel treatments and cure. The ultimate research target is to permit the interpretation of variants and reconciliation of the diagnosis with molecular findings. Such an eventuality will provide meaningful information to clinicians and provide useful counseling to patients. Thus, it is crucial for future studies to attempt an analysis and detailed mapping of the genes that contribute to the appearance and progression of each type of RP.

In addition, a detailed map of RP pathogenic genes could provide vital information for future research on RP genetics and therapy methods, particularly gene therapy. By presenting the major genes involved in RP pathogenesis, future therapy methods may focus on exact mutations and variants that provide accurate treatment by targeting specific loci.

ETHICS DECLARATIONS

Ethical approval: This study was an observational bibliographic study and no ethical approval was required.

Conflict of interest: The authors have no conflicts of interest to declare.

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