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IP International Journal of Ocular Oncology and Oculoplasty

Journal homepage: www.ipinnovative.com

Review Article

Recent Developments on the major genes involved in retinitis pigmentosa

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ARTICLE INFO

Article history:
Received 13-08-2020
Accepted 28-08-2020
Available online 03-09-2020

Keywords:
Autosomal dominant
Autosomal recessive
Genes
Retinitis pigmentosa (RP)
Xlinked RP

ABSTRACT

Retinitis pigmentosa (RP) is a common retinal dystrophy that affects millions of individuals, of both sexes, worldwide. The age of onset and the phenotypic characteristics vary between patients of different ethnicities. It may be syndromic when it coexists with several syndromes, like Usher syndrome, or non-syndromic. It follows autosomal dominant, autosomal recessive or X-linked inheritance. RP is genetically heterogeneous with, approximately, one hundred genes identified to date. The present mini review includes articles about the pathogenesis of syndromic and non-syndromic RP. Eighty-seven papers written in English and published in the last decade, about the pathogenesis of RP were reviewed and analyzed in order to summarize and highlight the major genes implicated in RP. We identified more than 80 genes associated with syndromic and 30 genes with non-syndromic RP. Among them RHO and RPGR, followed by PRPH2, PRPF31 and RP2 are the major genes involved in RP.

1. Introduction

Retinitis pigmentosa (RP) is the most common type of retinal dystrophy.[1–5] affecting millions of individuals around the world.[6] It was first described by A.C. van Trigt in 1853, while F.C. Donders was the first that recognized this clinical condition in 1857.[7] It is characterized by abnormalities of rods and cones, the photoreceptors of the retina, initially of the middle periphery of the retina and progressively reaching the central retina.[2,5–7]

The age of onset varies among different patients, but usually it ranges from early childhood to mid-adulthood.[7,8] It may affect the clinical manifestations as early RP onset appears mostly with rapid progress, while other patients remain asymptomatic until the fifth decade of life.[7] The first symptom of RP is usually nyctalopia (night blindness) and difficulties in dark to light and light to dark adaptation.[1,5,9] Dyschromatopsia and blue-yellow defects color vision may be present in advanced cases of RP, whereas in other patients color vision may be normal.[5,7] Also, photopsia, photophobia, myopia and hyperopia are often presented in RP patients.[7] Progressive vision loss, often leading to tunnel vision or blindness characterizes advanced RP.[1] The retinal findings also include bone-spicule formations and attenuation of blood vessels, a waxy pallor of the optic nerve, shortening of the photoreceptor outer segments and abnormal ERG.[7]

RP may be accompanied with multiple clinical conditions including nystagmus, refractive error, macular hole, epiretinal membrane, cystoid macular edema, posterior subcapsular cataract, secondary retinal vasoproliferative tumors, vitreous cysts and optic nerve head and fiber layer drusen.[7]

The present review included articles about the pathogenesis of syndromic and non-syndromic RP by searching the PubMed and the Google Scholar databases.

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https://doi.org/10.18231/j.ijooo.2020.036

Only papers published in the last decade and written in English were selected and analyzed. Keywords used in this review were "retinitis pigmentosa", "genes", "autosomal dominant", "autosomal recessive", "X-linked RP". In total, 87 articles were reviewed and analyzed. Most scientifically recognized and recent papers were selected and focused in the review. The present article attempts to summarize and highlight the major genes implicated in the pathogenesis of autosomal dominant, autosomal recessive and X-linked RP.

2. Epidemiology of RP

RP may appear as syndromic (20-30% of all cases), when it is accompanied with systemic manifestations including developmental abnormalities and neurosensory disorders, and non-syndromic (70-80% of all cases), without other clinical manifestations.[9] The prevalence of non-syndromic RP varies from 1:9000 to 1:750.[7]

RP also appears as autosomal dominant RP (adRP) in 20-40% of all cases (better prognosis), autosomal recessive RP (arRP) in 30-50% of all cases and X-linked RP (xlRP), the most severe form, in 5-15% of all cases.[1–4] Digenic, mitochondrial and de novo mutations have been also reported,[3,4] whereas sporadic RP exhibits in almost 30% of all cases.[1,3] RP also appears more severe among males.[10]

Approximately 30 different syndromes may provoke RP. The most frequent syndromes are Usher, Bardet-Biedl syndrome (BBS), Bassen-Kornzweig syndrome (abetalipoproteinemia), Refsum's disease and α-tocopherol transport protein deficiency.[9] Usher syndrome is associated with 10-20% of all syndromic RP cases affecting 1:12,000 to 1:30,000 in different populations.[11] 12-15 genes implicated with Usher syndrome may also be responsible for RP. Among them USH2A (1q41), MYO7A and (11q13.5), are the most important or better described to date.[9]

Syndromic RP is also appeared in BBS, which is inherited in an autosomal recessive manner. 5-6% of all RP cases are associated with BBS,[9] which is characterized by fundus abnormalities, pigmentary retinal dystrophy, and systemic manifestations including kidney disease, polydactyly, obesity, female genitourinary malformations and developmental delay.[11] The manifestations may be different among patients depending on the specific gene and the specific mutation within the gene that is affected.[7]

There are twenty one genes implicated with BBS, most of which may be associated with syndromic RP. Again, among them BBS1 (11q13), TTC8/BBS8 (14q32.11) and CEP290/BBS14 (12q21.32), are the most important or better described to date. However, approximately 30% of BBS cases have not been associated with any identifiable mutation in any of these genes.[11,12]

3. Genetic aspects of RP

At a genetic level it is reported that RP is complicated and heterogeneous,[1,2] whereas more than 80 genes are implicated with non-syndromic RP and more than 30 genes with syndromic RP.[3,6,7] These genes are mostly associated with metabolic functions of the neuroretina and/or RPE and especially the function of the photoreceptor.[13]

The first identified gene was RHO gene, whereas every year new genes are reported to be implicated with different RP subtypes.[7] It seems that there are more than 3100 mutations associated with non-syndromic RP,[2,3,6] whereas 1200 mutations are implicated with Usher and BBS syndromes. Except for the genetic heterogeneity, it seems that mutations in the same gene or even the exact same mutations may provoke different phenotypes among different patients.[6] This may be associated with the role that several genetic and/or environmental factors may have in the phenotypic expression of RP.[7] Moreover, although new mutations are reported to be at the same rate worldwide there are differences in the prevalence of some RP mutations among different populations. Interestingly, RHO mutations accounts for 30% of Americans of European origin, but only 10% in Chinese patients. On the other hand, RPGR mutations are presented with the same prevalence in RP patients worldwide.[14]

Worldwide databases are suggesting that there are twenty seven genes responsible for adRP, fifty five for arRP and six for xlRP,[1,15] including genes implicated with both adRP and arRP, such as BEST1, IMPDH1, NRL, NR2E3, RHO, RPE65 and RP1, and genes implicated with RP and macular degeneration including ABCA4, PRPH2, PRPF31 and C8orf37.[1] Also, other genes are implicated in both RP and Leber congenital amaurosis (LCA) (i.e., CRB1, CRX, RPE65, IMPDH1) while others are implicated in both RP and cone-rod dystrophy (CRD) (i.e., ABCA4, C8orf37, RPGR, CRX, PROM1).[2,6]

The most prevalent genes that cause adRP are RHO (26% of all cases), RP1 (6% of all cases) and PRPF31 (5% of all cases).[16] adRP genes cause approximately 50-75% of RP cases, depending on the populations screened.[14] However, it is difficult to screen efficiently the mutations implicated with adRP as some mutations reported may be proved to be nonpathogenic and novel mutations that are associated with adRP pathogenesis have not as yet included in the public domain.[6] Tables 1 and 2 report the major genes that are implicated in either both arRP and adRP or adRP in particular.

Among the putative fifty five genes that are implicated in arRP pathogenesis and thought to cause 2-5% of all cases, RPE65 (1p31.2), PDE6B (4p16.3), ABCA4 (1p22.1), CRB1 (1q31.3), USH2A (1q41), C2orf71 (2p23.2), RHO (3q22.1), PROM1 (4p15.32), TULP1 (6p21.31), C8orf37 (8q22.1), NRL (14q11.2), SPATA7 (14q31.3), are the most important or better described to date.[11,12]

Table 1: Genes implicated both in autosomal dominant and recessive RP pathogenesis

GENE [11,12,14]	**Chromosome**	**Other Diseases**
BEST1 [11,12,14]	11q12.3	Leber congenital amaurosis
NR2E3 [11,12,14]	15q23	Goldmann–Favre, enhanced S-cone syndrome
NRL [11,12,14]	14q11.2	
RHO [11,12,14]	3q22.1	Congenital stationary night blindness
RP1 [11,12,14]	8q12.1	
RPE65 [11,12,14]	1p31.2	Leber congenital amaurosis

Table 2: Genes implicated in autosomal dominant RP pathogenesis

Gene [11,14]	**Chromosome**	**Other diseases**
CA4 [11,14]	17q23.2	
CRX [11,14]	19q13.32	Leber congenital amaurosis, Cone–rod dystrophy
FSCN2 [11,14]	17q25.3	
GUCA1B [11,14]	6p21.1	Macular dystrophy
HK1 [11,14]	10q22.1	
IMPDH1 [11,14]	7q32.1	Leber congenital amaurosis
KLHL7 [11,14]	7p15.3	
OR2W3 [11,14]	1q44	
PRPF3 [11,14]	1q21.2	
PRPF6 [11,14]	20q13.33	
PRPF8 [11,14]	17p13.3	
PRPF31 [11,14]	19q13.42	
PRPH2 (RDS) [11,14]	6p21.1	Adult vitelliform macular dystrophy, Cone–rod dystrophy, Central areolar choroidal dystrophy
RDH12 [11,14]	14q24.1	Leber congenital amaurosis
ROM1 [11,14]	11q12.3	RP with macular degeneration
RP9 [11,14]	7p14.3	
SEMA4A [11,14]	1q22	Cone–rod dystrophy
SNRNP200 [11,14]	2q11.2	
SPP2 [11,14]	2q37.1	
TOPORS [11,14]	9p21.1	

Table 3: Genes implicated in X-linked RP pathogenesis

GENE [6,17]	**Chromosome**	**Other diseases**
OFD1-RP23 [6,17]	Xp22.2	
RP2 [6,17]	Xp11.23	
RP6 [6,17]	Xp21.3-p21.2	
RP24 [6,17]	Xq26-q27	
RP34 [6,17]	Xq28-qter	
RPGR	Xp11.4	Macular dystrophy, Cone dystrophy, Atrophic macular degeneration, Leber congenital amaurosis

Finally, there are six loci implicated in xlRP.[6,17] Most xlRP cases are associated with RPGR mutations (70-90%), whereas RP2 mutations also account for 6-20% of xlRP cases.[17] Mutations in the ORF15 region are implicated in 30-60% of xlRP cases. Approximately 80% of xlRP cases are associated with RPGR and RP2 mutations indicating that these genes may be target candidates for gene therapy or other therapeutic approaches.[11] Table 3 reports the major genes that are implicated in xlRP.

4. Diagnostic approach of RP

It must be stretched that the genetic heterogeneity makes the genotype-phenotype correlation difficult, although genetic and molecular diagnosis may be crucial for the genetic counseling and the selection of the appropriate management.[3] There are several methods used for the detection of mutations implicated with several inherited diseases like RP, including deletion detection, linkage mapping and subclone sequencing.[14] Also, specific genotyping microarrays and the gene-by-gene analysis with Sanger sequencing are used for mutation screening. New technologies like next-generation sequencing (NGS) provide the chance to screen effectively RP patients, as high sensitivity and efficiency are significant characteristics of this method, although the disease is genetically heterogeneous.[3] Moreover, new techniques such as, targeted retinal-gene capture NGS, whole-exome NGS and whole-genome NGS may be important in mutation screening. The aim of effective genetic testing is to incorporate genetic information into clinical care and counseling. Thus, the management of several genetic disorders may be based on the results of such methods.[14]

As mentioned above, RP is characterized by extremely high genetic heterogeneity. This, characteristic provoked a great many attempts to map and analyze the genes and the mutations that provoke and progress different types of RP. Below we review the major genes responsible for adRP, arRP and xlRP as well some other important genes implicated in the pathogenesis of the main RP types.

5. Major GENES involved in adRP, arRP and xlRP Pathogenesis

5.1. RHO GENE

RHO gene (RP4, Retinitis Pigmentosa 4, Opsin-2) which belongs to the GPCR (G protein coupled receptors) family of genes, is located on 3q22.1 chromosome and encodes rhodopsin - the protein mostly associated with rods.[6,15] It is comprised of 348 amino acids with 7 transmembrane domains, a luminal N terminus and a cytoplasmic C terminus. It also has 11-cis-retinal attachment site (lys296), a site significant for active rhodopsin. The inner segment of rod photoreceptors synthesizes rhodopsin, which mediates vision in dim light.[15]

The most frequent gene accounting for 20-30% of adRP cases is RHO.[2,3,6,15] There are approximately 150 mutations in RHO associated with RP worldwide. Characteristically, p.P23H which is estimated to be responsible for 12% of RP cases in USA was the first gene defect reported.[13,14] The prevalence of RHO mutations in adRP differs among different populations. It is estimated to be between 16% and 35% in Western population. Many adRP cases associated with RHO mutations have been also reported in Israeli and Palestinian populations,[18] in Spanish,[19] Japanese,[20] Korean,[21] and Iranian[22] patients. Moreover, more severe cases have been reported in Swedish families.[16]

In addition, RHO has been also implicated with the pathogenesis of arRP, although only few cases have been reported.[13,15] Most arRP cases associated with RHO gene mutations have been identified in Chinese families, whereas p.P347L is thought to be the most common mutation.[15]

6. RPGR GENE - RP2 GENE

The RPGR gene which is localized on chromosome Xp11.4,[6,23] is associated with 70-90% of xlRP cases. In addition 6-20% of xlRP cases are related with RP2 gene mutations and a lower percent with mutations in the OFD1 gene. ORF15 is the RPGR exon that has most disease associated mutations, accounting for approximately 50-60% of all cases.[10,24] More specifically, mutations in this exon have been associated with several X-linked retinal degenerations including xlRP, macular dystrophy, cone dystrophy (CD) and atrophic macular degeneration.[6,10,23–25] Most ORF15 mutations are frameshift mutations, resulting in truncated products of this exon and affect ORF15 glutamylation.[10,24] In addition, mutations in exon ORF15 and TTLL5 gene contribute to a common disease pathway.[17]

It is reported that a large deletion in RP2 and 4 frameshift mutations in RPGR caused xlRP in Chinese patients.[10] Similarly, there are xlRP cases among Jordanian, Japanese or patients of other ethnicities with disease-causing mutation in RP2 or RPGR.[20,26] RPGR gene mutation may also cause LCA or RP of early onset, whereas in other benign cases visual acuity was stable until the age of forty.[27]

Males appear with nyctalopia and visual impairment, while carrier females have milder phenotypes, mainly characterized by various degrees of myopia.[23] In addition, RPGR variants have also been related with several systemic manifestations,[28] whereas blindness is estimated to be caused in 20% of these RP patients at approximately the age of 40.[29] Systemic manifestations may also contribute to the verification of several pathogenic variants.[28]

7. Other important genes involved in adRP and arRP pathogenesis

7.1. PRPH2/RDS GENE and ROM1 GENE

The PRPH2 gene which is located on 6p21.1, contains 3 exons and encodes peripherin 2, a glycoprotein of 39-kDa with 346 amino acids.[2,6] The ROM1 gene encodes rod outer-membrane protein 1, and along with PRPH2 gene is thought to be significant for the formation and function of rod and cone outer segments.[13]

PRPH2, also known as retinal degeneration slow/RDS**,** is major causative gene of adRP and CRD.[19,25,27,30] More than 151 mutations have been identified in PRPH2, most of which may produce different RP phenotypes even among family members. Mutations in this gene may also cause secondary defects in tissues like choroid and retinal epithelium pigment.[31] indicating the role of this gene in RP.[13] PRPH2 mutations are associated with adRP, autosomal dominant macular degeneration,[1,6] macular pattern dystrophies[13] and autosomal dominant Stargardt disease -like phenotypes.[32] There are also cases of dominant adult onset vitelliform macular dystrophy carrying mutations in PRPH2 gene.[2,33]

Although, there is no absolute linkage between ROM1 mutations and monogenic adRP,[31] there are cases of autosomal digenic RP in patients heterozygous for both a PRPH2 mutation and a ROM1 mutation.[2,6,34] However, there are individuals appearing with ROM1 alterations in the absence of PRPH2 mutations.[13] The appearance of different phenotypes in patients with mutations in the same gene remains under investigation.[35–37] Characteristically, there are cases where genes modify the PRPH2 phenotypes, including the role of ROM1 in PRPH2/ROM1 digenic RP and the interaction of ABCA4 with PRPH2 in other cases.[31]

The prevalence PRPH2 gene mutations related adRP varies among different populations, ranging from 0% in Mexico to 4.7% in Belgium and 10.3% in France.[38,39] As a result this gene is estimated to be the second major gene for adRP pathogenesis, next to RHO, in Western populations. Some major mechanisms degrading the expression of PRPH2 protein are sequence variants, aberrant mRNA splicing, problems in protein localization, and protein degradation.[38]

8. PRPF31, PRPF3, PRPF8 and SNRNP200 GENEs

PRPF31 gene, which is located on chromosome 19 (19q13.42),[2] consisting of 14 exons and encoding a 499 amino acids protein is estimated to be the third, next to RHO and PRPH2 genes, major causative gene of adRP.[40] Over forty PRPF31 gene mutations have been identified in adRP patients, whereas it may also be a causative gene of macular degeneration.[1] Moreover, PRPF31 disease-causing mutations cause different phenotypes, as some carriers are asymptomatic while others are blind. However, nyctalopia is mostly appeared from infancy to 4 years old.[40] Hence, genetic modifiers may be responsible for phenotypical variability.[16]

PRPF31's mutation prevalence in adRP differs among different populations ranging from 1% to 8%.[41] More specifically, in Europe the prevalence is estimated to be 6.7% while in the USA the frequency is around 5%.[16] On the other hand, PRPF31's mutations are very rare in East Asian population.[20]

PRPF3, PRPF8 and SNRNP200 which encodes processing factors 3,8 and 31, respectively, are important causative genes of RP.[2,4] More specifically, PRPF8 and SNRNP200 mutations are major causative genes in Belgium,[38] and may be responsible for about 38% of adRP cases according to several reports.[4]

PRPF3 gene (RP 18, SNRNP90) appears to be causative in three mutations: T494M which is implicated with adRP pathogenesis in families from America, Denmark, England, Japan, Korea, Spain, P493S which is associated with sporadic RP in Germany, UK and USA and A489D which mainly appears in Spain. However, these mutations are very rare in adRP patients in East Asia.[42]

9. PDE6 GENE

PDE6A, PDE6B and PDE6G are subunits form PDE6 complex. The PDE6 complex encodes a protein that contribute to the function of rod phototransduction. Hence, absence of PDE6 may provoke rode-cone devolution. Defects in rod-specific cyclic guanosine monophosphate (cGMP) phosphodiesterase 6 (PDE6) gene family which effect the phototransduction cascade are responsible for about 8% of diagnosed arRP cases. Absence of PDE6 may cause rod-cone degeneration, but the mechanism remains unclear.[12]

Each one of the subunits may also affect the function of photoreceptors. More specifically, mutations in PDE6A and PDE6B cause arRP, while heterozygous carriers are at great risk of visual impairments. On the contrary, PDE6G provoke early onset arRP.[12]

Mutations in PDE6B gene, which is localized on chromosome 4 (4p16.3), encoding cGMP phosphodiesterase beta subunit, are mostly associated with arRP.[6,43] Especially, these mutations are responsible for many arRP cases in specific ethnic groups, including Caucasians and Korean population.[21,44] These patients are characterized by early onset of RP, nyctalopia and photophobia,[43,45] whereas congenital stationary nyctalopia inherited in a dominant manner is also associated with PDE6B mutations.[6]

10. CRB1 GENE

The CRB1 gene is located on chromosome 1 (1q31.3), consists of twelve exons and eleven introns and encodes

2 extra-cellular signal proteins of 1376 and 1406 amino acids long.[6,46] It is thought to be very important for the development of the retina.[35,46]

To date, more than 200 mutation associated with arRP have been identified in CRB1.[35] It is estimated that patients with null mutations (i.e., nonsense mutations) on two alleles of CRB1 gene mostly present with more severe phenotypes including LCA, whereas milder phenotypes like RP may be caused after missense mutation on at least one allele.[47,48] CRB1 mutations may also cause various phenotypes including retinal dystrophies like RP, LCA, and CRD, or isolated macular dystrophy and foveal retinoschisis.[6,25,47,49]. Additionally, CRB1 mutations account for 3% to 9% of non-syndromic arRP[50] and 9-15% of LCA cases.[51] Also, childhood CRD with macular cystic degeneration and autosomal dominant Stargardt disease phenotypes appear frequently.[52] However, clinical variability in patients with same CRB1 mutations indicates that arRP associated with CRB1 may also be modulated by other factors.[53]

RP patients with CRB1 mutations are mostly characterized by gradual vision from mid periphery, progressive photoreceptor degeneration, hyperopia, visual impairment, and in severe cases blindness.[7,47].

CRB1 mutations mostly appear in Israel and Spain causing autosomal recessive retinal degeneration of early onset.[35,48] Moreover, many Thai families carry these mutations,[54] whereas it is estimated that in German patients with LCA mostly carry CRB1 mutations[55]. CRB1 mutations, have been also identified in Danish LCA patients (7%)[56], in Brazilian CRD patients[46],and Tunisian RP patients[57].

11. ABCA4 GENE

The ABCA4 gene is localized on chromosome 1 (1p13) and consists of fifty exons.[58]. It encodes an ATP-binding cassette (ABC) transporter protein which is mainly located on the rims of photoreceptor discs.[6,58–61] The role of this protein is significant during photo transduction as it transfers the phosphatidylethanolamine (PE) and the N-retinylidene-phosphatidylethanolamine (NRPE) from the lumen of the outer segment disc membranes of photoreceptors to the cytoplasmic leaflet. Thus, it protects the photoreceptors from toxic retinoid.[58,60,61]

There are over 800 ABCA4 mutations reported to be associated with RP. Although, these mutations may be deletions of several exons or only single base substitutions, most are missense mutations.[58] The phenotype may vary, depending on their effect on regulatory regions of the gene and the amino acid composition of the protein.[62] The variants are heterogeneous, while most are related with retinal dystrophies.[21,25] They may also cause autosomal recessive Stargardt disease, CD or CRD and arRP.[45,61–64] Characteristically, ABCA4 is the major causative gene for autosomal recessive Stargardt disease and arCRD,[65] while it also may cause Usher syndrome.[3,66] Homozygous or compound heterozygous arRP have been associated with twenty seven missense mutations, nine splicing mutations, four deletions, and a complex rearrangement.[67]

There are also significant differences among various ethnicities. Characteristically, mutation p.G1961E is estimated to be the most frequent one in European patients. On the other hand, p.A1773V and p.G818E are identified, respectively, in 17% and 15% of the cases in Mexico[63] but appear more frequently in RP patients from Europe and America[59].

12. PROM1 GENE

The PROM 1 gene is localized on chromosome 4 (4p15.32),[6,34,68] consists of twenty-seven exons and encodes prominin-1, a five-transmembrane domain glycoprotein[6,34]. Stem and progenitor cells from neural and hematopoietic systems mainly express prominin-1. Additionally, it is expressed by photoreceptor, glial, and epithelial cells of various adult organs. More specifically, PROM1 enhances disk membrane morphogenesis, as it is mostly found at the base of outer segments of photoreceptors.[68]

Over 35 mutations of the PROM 1 gene have been identified,[34] most of them implicated in several retinal degenerative phenotypes, like arRP affecting the macula, autosomal dominant Stargardt disease, autosomal dominant macular dystrophies with bull's eye and CRD.[1,69] However, probably there is a relationship between each mutation and the phenotype that is apparent. Characteristically, autosomal dominant Stargardt disease and macular dystrophy with bull's eye are associated with missense mutations, while nonsense mutations and frameshift mutations may cause RP, CRD or other forms of macular degeneration.[34,70]

There are many arRP cases reported in China and Thailand that are related with PROM1 mutations.[34] while recessive PROM1 mutations have been associated with progressive RP, affecting the macula, in Spanish families.[71]

13. RP1 GENE

RP1 gene (retinitis pigmentosa 1) is localized on chromosome 8 (8q12), contains 4 exons and encodes oxygen-regulated protein 1 with 2156 amino acids, which contributes to the development of rods and cons, the organization of outer segments and the regulation of photoreceptor microtubules.[72,73] RP1 gene mutations are implicated with both adRP and arRP[1,3,38], accounting for approximately 5.5% and 1% of cases, respectively.[73] These mutations usually cause RP with good prognosis,[72] whereas it is also reported that there is association with arCRD and autosomal recessive macular dystrophy.[74]

Over 150 mutations have been identified, mostly truncation variants. Deleterious effects of truncated RP1 protein seem to also have a major role. However, the effect of RP1 mutation on RP inheritance remains unclear.[73] Almost 3% of adRP cases in North America carry a nonsense mutation at codon 677 (p.R677). In addition, adRP-causing mutations have been also identified in patients from Spain,[19] Japan,[20] Korea.[21] and Iran,[22], whereas arRP-causing mutations have been identified in Spanish patients.[73]

14. RPE65 GENE

The RPE65 gene is localized on chromosome 1 (1p31.2), encodes a 65 kDa retinol isomerase called retinal pigment epithelium-specific protein which produces 11-cis retinal from all-trans retinol.[2,6,75] Over 100 mutations are associated with the pathogenesis of arLCA,[2,6,75–78] RP.[6,75–77] adult onset vitelliform macular dystrophy[79] and CRD.[80] Although it may produce both adRP and arRP, it is mostly associated with arRP.[75] RPE65 variants are mostly appeared in Caucasian populations, while high prevalence is also reported in India.[56] On the contrary, there are many adRP cases reported in Irish population,[75,79] 16% of LCA cases are also associated with RPE65 mutations.[80]

RPE65 mutations are mostly associated with retinal dystrophies, with recessive inheritance and loss of protein function. c.1430G>A (D477G) mutation may cause adRP affecting both choroid and macula, with delayed onset.[75] The phenotype varies, as there are mild or severe cases in carriers of D477G mutation, while central vision defect is a frequent manifestation. This characteristic differs from typical RP which is characterized by progressive vision loss from the periphery to the posterior pole.[79,81]

Some frequent manifestations of RP caused by RPE65 mutations are early onset, keratoconus, nystagmus, clumped pigment in later stages,[57] visual impairment, high hyperopia, night blindness, and photophobia during childhood.[82] Additionally, better prognosis characterizes cases where visual symptoms appear after infancy.[49]

15. USH2A GENE

The USH2A gene is localized in 1q41,[6] consists of 72 exons and encodes usherin, a protein with 5202 amino acids. Mutations in this gene may cause 10-15% of arRP cases and approximately half of the Usher type 2 cases. Barely 7% of RP patients in North America and 4% of Japanese arRP patients appear to carry such mutations, while the USH2A prevalence appears higher in Spanish patients[83] and Caucasian populations[84] and it is rare in Israeli[66] and arRP Korean patients[21]. However, the disease-causing mutations of the USH2A gene differ between various ethnicities[84]. It is noted that RP is mostly associated with mutations in USH2A and EYS in the Japanese population.[20,85] As these mutations may cause either non-syndromic RP or RP and Usher syndrome, hearing examination is vital in these patients[3]. Specific mutations are related with hearing loss related RP in China and Thailand.[86] Moreover, non-syndromic RP with late onset may be caused by USH2A mutations.[45]

16. CRX GENE

CRX gene is located on chromosome 19 (19q13.33), contains four exons and encodes a 299-amino acid homeodomain transcription factor.[2,6] CRX and NRL are genes implicated in RP pathogenesis, controlling the expression of photoreceptor cell specific genes. The mutations may affect the development of photoreceptor cells, causing photoreceptor cell degeneration[13] and leading to severely decreased visual acuity from the first year of life.[49] The phenotype of RP may be heterogeneous, with incomplete penetrance and influence by other genes[87]. CRX mutations are also implicated with ad, ar and de novo LCA, adCRD[2,6,13] and adRP.[27,76] Characteristically, CRX is thought to be the major causative gene in CRD[25,30]. Moreover, these mutations have been reported in Japanese arRP patients.[20]

17. Conclusions

RP is a retinal dystrophy characterized by extremely widepgenetic heterogeneity. Several different genes with variousmutations are implicated in RP, syndromic and/ornon-syndromic. Simultaneously, the same mutations could be associated with different phenotypes among patientseven of the same origin. Global literature reports that over 3000 mutations in approximately 100 genes havebeen identified in cases of non-syndromic RP and morethan 1200 mutation in syndromic RP cases. In addition, overlapping of clinical phenotypes may make difficult toverify particular genotype-phenotype correlation. Thus, itseems that RP diagnosis and genetic association withparticular mutations can be problematic.

However, it would promising if future research attempted to reveal all RP pathogenic mutations and relate them with precise phenotypic characteristics. Moreover, genetic diagnosis may provide significant information for the possibility of using gene therapy. Thus, better screening of disease causing mutations may provide the appropriate information for more effective clinical care and counseling.

18. Disclosure

Ethical issues have been completely observed by the authors. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. No conflict of

interest has been presented.

19. Acknowledgment

None.

20. Source of Funding

None.

21. Conflict of Interest

None.

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Cite this article: Loukovitis Eleftherios D , Stoimeni Anastasia A , Tranos Paris G , Koukoula Stavrenia Ch , Balidis Miltos O , Asteriadis Solon G , Vakalis Thanos N , Sousouras Thanasis Ch , Anogeianakis George A . **Recent Developments on the major genes involved in retinitis pigmentosa**. *IP Int J Ocul Oncol Oculoplasty* 2020;6(3):157-166.