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Review article

Retinitis Pigmentosa Genes Implicated in the Population of America: A Systematic Review

Olivia Margarita Narváez[1], Hugo Mendieta Zerón[2], Orlando Torres[3], Magally Escobar[4], Martha Liliana Trujillo-Güiza[4]

[1]*Santo Tomás University, Faculty of Optometry, Bucaramanga, Colombia*
[2]*Autonomous University of the State of Mexico (UAEMex) and "Mónica Pretelini Sáenz" Maternal-Perinatal Hospital, Faculty of Medicine, Toluca, Mexico*
[3]*Antonio Nariño University, Faculty of Veterinary Medicine, Bogotá, Colombia*
[4]*Antonio Nariño University, Faculty of Medicine, Bogotá, Colombia*

SUMMARY

Introduction/Aim. Retinitis pigmentosa (RP) is a diverse group of inherited retinal diseases characterized by the gradual degeneration of rod and cone photoreceptors in the retina. RP is primarily inherited, with numerous genetic mutations implicated in its pathogenesis. The aim of this study was to summarize the findings of studies related to genes implicated in retinitis pigmentosa, in autosomal dominant (adRP), autosomal recessive (arRP), and X-linked RP (xlRP) patients in America.
Material and Methods. In this comprehensive search of literature via the Medline/PubMed database, SciELO, Redalyc, ScienceDirect, and Google Scholar (English/Spanish), 75 articles between 2010-2020 were reviewed; the final analysis was based on 21 articles.
Results. The main gene mutations found in America for adRP were RHO (rhodopsin) and PRPF31 (pre-MRNA processing factor 31); for arRP, USH2A (usherin 2A) and EYS (eyes shut homolog); and for xlRP, RPGR (retinitis pigmentosa GTPase regulator) and RP2 (retinitis pigmentosa 2).
Conclusion. Most of the genes currently found worldwide to cause RP were present in America, with similarities and differences with other populations in Asia and Europe.

Keywords: **autosomal dominant, autosomal recessive, inheritance pattern, retinitis pigmentosa, X-linked**

Corresponding author:
Hugo Mendieta Zerón
e-mail: mezh_74@yahoo.com

INTRODUCTION

Retinitis pigmentosa (RP) is a diverse group of inherited retinal diseases (IRDs) characterized by the gradual degeneration of rod and cone photoreceptors in the retina. RP is one of the leading causes of visual impairment, affecting approximately 1 in 3,000–7,000 individuals globally, though prevalence varies by region. Orphanet (1) reports a global prevalence of 1-5 per 10,000 people. The primary symptoms include night blindness and narrowing of the visual field, often progressing to a concentric pattern known as tunnel vision. In the early stages, rod photoreceptors are primarily affected; as the disease advances, cone involvement leads to deficits in visual acuity, color perception, and spatial detail recognition. Typical fundus findings include bone spicule pigmentation, thinning of retinal vessels, and a waxy appearance of the optic disc. Retinal changes are also evidenced by abnormal electroretinogram results and structural alterations detectable via optical coherence tomography. RP can present in two forms: syndromic, where it is part of a broader systemic condition, and non-syndromic RP, where it affects only the eyes. Clinical manifestations vary depending on the specific genetic mutations involved (2-4).

RP is primarily inherited, with numerous genetic mutations implicated in its pathogenesis. Over 3,000–4,000 mutations across more than 80 genes are associated with non-syndromic RP (2-4), while mutations in 31 genes are linked to the syndromic form (5). Usher syndrome and Bardet-Biedl syndrome are the most frequently associated syndromic conditions. The majority of RP cases are caused by monogenic mutations (2), typically affecting photoreceptors or the retinal pigment epithelium (6).

Based on the mode of inheritance, RP is classified as autosomal dominant (adRP), autosomal recessive (arRP), X-linked (xlRP), mitochondrial, or of unknown inheritance pattern (2, 5). Certain genetic mutations associated with RP are also linked to other IRDs. Globally, the most frequently reported genes associated with RP include USH2A (usherin), RHO (rhodopsin), and RPGR (retinitis pigmentosa GTPase regulator) (7), particularly adRP. The primary genes implicated in adRP are RHO, RPRF (rapidly progressive renal failure), PRPH2 (peripherin 2), RP1 (retinitis pigmentosa 1), IMPDH1 (Inosine-5'-monophosphate dehydrogenase 1), and PRPF8 (pre-mRNA processing factor 8). For arRP, the most commonly involved genes include USH2A, ABCA4 (ATP-binding cassette subfamily A member 4), PDE6A (phosphodiesterase 6A), PDE6B (phosphordiesterase 6B), and RPE65 (retinoid isomerhydrolase). In xlRP, RP1 and RPGR are the principal genes (2).

Although the genetic characteristics and mutations in RP have been extensively documented worldwide, there is limited and outdated information available for the Americas, particularly Latin America, with some studies being over a decade old. Currently, there is no approved treatment for RP, which highlights the importance of identifying the specific causative gene in affected individuals. This is especially relevant as pharmaceutical companies and research institutions are increasingly focusing on clinical trials aimed at developing therapies to treat or slow the progression of the disease. This review aims to summarize the genes associated with adRP, arRP, and xlRP in the Americas.

MATERIAL

Search

This systematic review was carried out between October and December 2020. Studies published from 2012 to 2020 that reported genetic mutations associated with RP in North American and Latin American populations were considered eligible for inclusion. The review outlines the current state of research on the genetic characterization of RP, drawing from academic databases including MEDLINE, PubMed, SciELO, Redalyc, ScienceDirect, and Google Scholar. Articles published in English and Spanish were included. Based on the selected studies, several tables were created to organize genetic information and list the authors of relevant publications.

The search strategy was structured around the topics of interest, methodologies used, and target populations. The following search terms and descriptors (MeSH, DeCS) were used: “retinitis pigmentosa,” OR “retinosis pigmentaria,” OR “inherited retinal dystrophies,” OR ("retinitis pigmentosa/epidemiology"[Mesh], OR "retinitis pigmentosa/etiology"[Mesh], OR "retinitis pigmentosa/genetics"[Mesh], OR "retinitis pigmentosa/statistics and numerical data"[Mesh]), AND “retinitis pigmentosa/genetics,” OR “retinitis pigmentaria/ genética,” AND “retinitis pigmentaria/autosomal dominant,”

AND "retinitis pigmentaria/autosomal recessive," AND "retinitis pigmentaria/X-linked," AND "retinitis pigmentaria/non-syndromic," "retinitis pigmentaria/America," OR "retinosispigmentaria/America". These terms were applied to full-text searches or topic-based queries, depending on the options available in each database.

Ethics

The study protocol was approved by the Ethics Research Committee of Ciprés Grupo Médico (2020-09-02), Toluca, Mexico. Informed consent was not required, as the data were derived from previously published studies.

Eligibility criteria

This review included studies that identified genes associated with syndromic or non-syndromic RP in patients from the American continent. Studies were required to have clearly defined clinical diagnostic criteria for RP (3) and to use reliable and conclusive genetic testing methods. Additional relevant articles cited within selected studies were also retrieved. Reference lists were reviewed to identify any additional publications not captured by the initial search.

Studies were excluded if they focused on mitochondrial or unknown inheritance patterns of RP or reported findings related to other IRDs. Articles that did not meet the inclusion criteria based on their titles and abstracts were also excluded.

RESULTS

General findings

Out of 75 studies initially identified, 21 articles were included in the review, while 54 were excluded after evaluating their abstracts and full texts. Of the selected articles, 57% originated from North America, 14% from Colombia, 10% each from Brazil and Cuba, and 5% from Mexico and Venezuela, respectively. The specific disorders covered are detailed below.

Autosomal dominant RP

Eighteen genes were identified in association with the adRP inheritance pattern. The RHO (rhodopsin) gene was reported in four countries: Brazil, Colombia, Mexico, and North America. The SNRP200 gene was found in Brazil and North America. BBS1, PRPF31, and PRPF8 were reported in both Brazil and Mexico, while TOPORS was identified in Mexico and North America. In Brazil and North America, the highest number of adRP-related genes (61% and 50%, respectively) was reported, followed by Mexico (33%) and Colombia (17%). Among the most frequently reported genes were RHO, PRPF31, and SNRP200. In syndromic forms, the BBS1gene was identified in 7.23% of cases (Table 1). A detailed list of syndromic and non-syndromic RP-related genes identified in the American population is provided in Table 2.

Table 1. *Autosomal dominant retinitis pigmentosa mutations in America*

Gene	Probands (n)/Country	Percentage
CRX (Cone rod homeobox).	1 (Brazil) (8)	1.20
PDE6B (Phosphodiesterase 6 B)	5 (Brazil) (8)	6.02
PROM1 (Prominin 1)	2 (Brazil) (8)	2.41
RIMS1 (Regulating synaptic membrane exocytosis 1)	1 (Brazil) (8)	1.20
ROM1 (Retinal outer segment membrane protein 1)	1 (Brazil) (8)	1.20
BBS1 (Bardet-Biedl syndrome 1)	6 (Brazil) (8)	7.23
RP1 (Retinitis pigmentosa 1)	1 (Mexico) (9)	1.20
IMPG1interphotoreceptormatrixproteoglycan 1	1 (North America) (10)	1.20
IMPDH1 (Inosine monophosphate dehydrogenase 1)	1 (Canada) (11)	1.20
	1 (North America) (10)	-
EFTUD2 elongation factor Tu GTP binding domain containing 2	(North America) (12)	0.00
RHO (Rhodopsin)	6 (Brazil) (8)	24.10
	11 (Canada) (11)	
	N/R (Colombia) (13)	
	3 (Mexico) (14)	

SNRP200 (Putative U5 small nuclear ribonucleoprotein 200 k Da helicase)	4 (Canada) (11)	9.64
	4 (Brazil) (8)	
PRPH2 (Peripherin 2)	3 (Canada) (11)	7.23
	N/R (Colombia) (13)	
	3 (Brazil) (14)	
PRPF31 (Pre-mRNA processing factor 31)	2 (Canada) (11)	22.89
	6 (Brazil) (9)	
	3 (Mexico) (9)	
	5 (North America) (10)	
	3 (North America) (15)	
NR2E3 (nuclear receptor subfamily 2 group E member 3)	2 (Brazil) (8)	4.82
	2 (Mexico) (9)	
NRL (Neural retina leucine zipper)	1 (Mexico) (9)	1.20
	N/R Colombia (13)	
PRPF8 (Pre-mRNA processing factor 8)	3 (Brazil) (8)	4.82
	1 (Mexico) (9)	
TOPORS (TOP1 binding arginine/serine-rich protein)	1 (Mexico) (9)	2.41
	3 (Canada) (11)	
	83	100.00

N/R: not reported

Table 2. *Autosomal dominant retinitis pigmentosa. Syndromic and no syndromic genes identified in the American population*

Gene	Nucleotide variant	Protein variant-exon	# Families	# patients/n	Country
CRX (Cone rod homeobox).	Not reported	Not reported	1,159	1,246 (121 with RP) n =1	Brazil (8)
	122 G → A 436_447del	Arg41Gln Leu146_Pro149del	200	n=2	North America (8)
RDS			200	n=18	North America (8)
RP1			200	n=7	North America (8)
PDE6B (Phosphodiesterase 6 B)	Not reported	Not reported	1,159	1,246 (121 with RP) n= 5	Brazil (8)
PROM1 (Prominin 1)	Not reported	Not reported	1,159	1,246 (121 with RP) n=2	Brazil (8)
RIMS1 (Regulating synaptic membrane exocytosis 1)	Not reported	Not reported	1,159	1,246 (121 with RP) n=1	Brazil (9)
ROM1 (Retinal outer segment membrane protein 1)	Not reported	Not reported	1,159	1,246 (121 with RP) n=1	Brazil (10)
BBS1 (Bardet-Biedl syndrome 1)	Not reported	Not reported	1,159	1,246 (121 with RP) n=6	Brazil (11)
RP1 (Retinitis pigmentosa 1)	c.2029C>T	p. Arg677Ter	Not reported	143, n=1	Mexico (10)
IMPG1interphotoreceptor matrix proteoglycan 1	c.T1823C	p. L608P	Not reported	35, n=1	North America, Hispanic probands (12)
IMPDH1 (Inosine monophosphate dehydrogenase 1)	c.954G>C	p.Q318H, exon 9	60	60, n =1	Canada (French Canadian Population) (8)
	c.612_614delTTC	p. K206del	Not reported	35, n=1	North America, Hispanic probands (11)
	676 G → A	Asp226Asn	200	n=5	North America (13)

EFTUD2 elongation factor Tu GTP binding domain containing 2	Not reported	p. Arg220Cys p. Ile80Leu p. Thr272Ala	Not reported	Not reported	North America (14)
RHO (Rhodopsin)	Not reported	Not reported	1,159	1,246 (121 with RP) n=6	Brazil (11)
	c.403C>G c.809G>T c.1031A>C c.151G>C c.541G>A c.553T>G	p.R135G, Exon 2 p.S270I, Exon $ p.Q344P, Exon 5 p.G51R, Exon 1 p.E181K, exon 3 p.C185R, exon 3	60	60, n=11	Canada (French Canadian Population) (8)
	genomic Localization: 3q21-q24	Rhodopsin	Not reported	Not reported	Colombia (11)
	c.491C>A c.557C>G	p. Ala164Glu p. Ser186Trp	Not reported	143, n=3	Mexico (13)
			200	n=53	North America (14)
SNRP200 (Putative U5 small nuclear ribonucleoprotein 200 k Da helicase)	c.2122G>A c.2041G>T c.3260C>T	p.V708I, exon 16 p.R681C, exon 16 p.S1087L, exon 25	60	60, n=4	Canada (French Canadian Population) (11)
	Not reported	Not reported	1,159	1,246 (121 with RP), n=4	Brazil (8)
PRPH2 (Peripherin 2)	c.554T>C	p.L185P, exon 1	60	60, n=3	Canada (French Canadian Population) (9)
	6p21.2-cen	Peripherin	Not reported	Not reported	Colombia (10)
PRPF31 (Pre-mRNA processing factor 31)	54618847del C c.862C>T	54618847del C p.R288W, exon 9	60	60, n=2	Canada (French Canadian Population) (15)
	Not reported	Not reported	1,159	1,246 (121 with RP), n =6	Brazil (8)
	c.682G>C c.866_879 del GGAAAGCGGC CCGG	p. Ala228Pro p. Arg289ProfsTer30	Not reported	143, n=3	Mexico (9)
	c.A172T c.866_879 del GGAAAGCGGC CCGG c.322+ 4_322+ 7delAGTG chr19:54632400, C> A	p.K58 p. R289Pfs*30) 5´terminal of intron 5	Not reported	35, n=5	North America (9)
			200	n=11	North America (13)
NR2E3 (Nuclear receptor subfamily 2 group E member 3)	Not reported	Not reported	1,159	1,246 (121 with RP), n=2	Brazil (8)
	c.166G>A	p. Gly56Arg	Not reported	143, n= 2	Mexico (9)
NRL (Neural retina leucine zipper)	c.148 T>C	p. Ser50Pro	Not reported	143, n=1	Mexico (9)
	14q11.2	NRL	Not reported	Not reported	Colombia (11)
PRPF8 (Pre-mRNA processing factor 8)	Not reported	Not reported	1,159	1,246 (121 with RP), n=3	Brazil (8)
	c.6928 A>G	p. Arg2310Gly	Not reported	143, n=1	Mexico (8)
			200	n=6	North America (8)
TOPORS (TOP1 binding arginine/serine-rich protein)	c.2554_2557delGA GA	p. Glu852GlnfsTer13	Not reported	143, n=1	Mexico (8)
	c.2666A>C c.2474_2475insA	P. H889R p. Y825X	60	60, n= 3	Canada (French Canadian Population) (8)

Autosomal recessive RP

In cases of arRP, 45 genes were identified. The USH2A gene was reported in four countries: Brazil, Colombia, Cuba and Mexico. Additionally, the genes CDHR1, CERKL, CRB1, MERTK, PDE6A, and RDH12 were detected in both Brazil and Mexico. The WDR19 gene was identified in Brazil and North America, while ABCA4 was reported in Mexico and North America. Brazil accounted for the highest number of arRP-related genes (53.4%), followed by Mexico (41.8%), North America (21%), Cuba (11.6%), and Colombia (4.6%). In Venezuela (2.33%), the MYO7A gene was associated with the Usher syndrome. The most frequently reported gene mutations in arRP were USH2A, EYS, and MYOTA (Table 3). A summary of the syndromic and non-syndromic genes identified in the American population is presented in Table 4.

Table 3. *Autosomal recessive retinitis pigmentosa mutations in America*

Gene	Probands (n)/Country	Percentage
BBS1 (Bardet-Biedl syndrome 1)	1 (Brazil) (8)	0.53
BBS2 (Bardet-Biedl syndrome 2)	1 (Brazil) (8)	0.53
CDHR1 (cadherin related family member 1)	1 (Brazil) (8)	0.53
CNGA1 (cyclic nucleotide-gated channel subunit alpha 1)	1 (Brazil) (8)	0.53
CNGB1 (cyclic nucleotide-gated channel subunit beta 1)	1 (Brazil) (8)	0.53
EYS (Eyes shut homolog)	1 (Brazil) (8)	8.42
	15 (North America)(16)	
GPR98†	1 (Brazil) (8)	0.53
HGSNAT (heparan-alpha-glucosaminide N-acetyltransferase)	2 (Brazil) (8)	1.05
RP1 (retinitis pigmentosa 1)	7 (Brazil) (8)	3.68
DHDDS dehydrodolichyldiphosphate synthase subunit	3 (North America) (17)	1.58
MKS1 (transition zone complex subunit 1)	1 (Brazil) (8)	0.53
PRPH2 (Peripherin 2)	1 (Brazil) (8)	0.53
ABHD12 (Abhydrolase domain containing 12, lysophospholipase)	1 (Brazil) (8)	0.53
MYO7A (Myosin7A)	8 (Brazil) (8)	5.79
	3 (Venezuela) (18)	
TULP1 (TUB like protein 1)	1 (Brazil) (8)	0.53
SAG S-antigen visual arrestin	N/R (North America) (19)	0.00
WDR19 (WD repeat domain 19)	1 (Brazil) (8)	0.53
	1 (North America) (10)	0.53
CDH23 (Cadherin -related 23)	N/R (Cuba) (20)	0.00
ADGRV1 (adhesion G protein-coupled receptor V1)	N/R (Cuba) (20)	0.00
PCDH15 (protocadherin related 15)	4 (Cuba) (20)	2.11
RP1 retinitis pigmentosa 1	1 (North America) (10)	0.53
ABCA4 (ATP binding cassette subfamily A member 4)	N/R (Mexico) (9)	1.05
	1 (North America) (10)	
	1 (North America) (21)	
ARL6 (ADP ribosylation factor like GTPase 6)	N/R (Mexico) (9)	0.00
PCARE (photoreceptor cilium actin regulator)	N/R (Mexico) (9)	0.00
CLN3 (CLN3 lysosomal/endosomaltransmembrane protein, battenin)	1 (Mexico) (9)	0.00
RDH5 (retinol dehydrogenase5)	1 (Mexico) (9)	0.53
RP2 (retinitis pigmentosa 2)	2 (Mexico) (9)	0.00

RPE65 (retinoidisomerohydrolase RPE65)	1 (Mexico) (9)	0.53
SPATA7 (spermatogenesis associated 7)	1 (Mexico) (9)	1.05
BBS10 (Bardet-Biedlsyndrome 10)	1 (Colombia) (22)	0.53
GNAT1 (G protein subunit alpha transducin 1)	1 (Mexico) (9)	0.53
IFT140 (intraflagellar transport 140)	1 (Mexico) (9)	0.53
IMPG2 (interphotoreceptor matrix proteoglycan 2)	1 (Mexico) (9)	0.53
FAM161A (FAM161 centrosomal protein A)	4 (North America)(17)	0.53
USH2A (Usherina 2A)	21 (Brazil) (8)	42.63
	7 (Colombia) (23)	
	N/R (North America) (24)	
	26 (Colombia) (23)	
	11 (Cuba) (20)	
	11 (Cuba) (25)	
	4 (Mexico) (10)	
	1 (North America) (9)	
CLRN1 (Clarin 1)	2 (Cuba) (20)	1.58
	1 (Brazil) (8)	
CDHR1 (cadherin related family member 1)	1 (Brazil) (8)	1.05
	1 (Mexico) (9)	
CERKL (Ceramide Kinase Like)	7 (Brazil) (8)	4.21
	1 (Mexico) (9)	
CRB1 (Crums cell polarity complex component 1)	5 (Brazil) (8)	3.68
	2 (Mexico) (9)	
MERTK (MER proto-oncogene, tyrosine kinase)	6 (Brazil) (8)	3.68
	1 (Mexico) (9)	
PDE6A (Phosphodiesterase 6 A)	2 (Brazil) (8)	2.11
	2 (Mexico) (9)	
PDE6B (Phosphodiesterase 6 B)	1 (North America) (10)	0,53
RDH12 (Retinol dehydrogenase 12)	3 (Mexico) (9)	2.63
	1 (Brazil) (8)	
	1 (North America) (10)	
	190	100

N/R: Not reported

Table 4. *Autosomal recessive retinitis pigmentosa. Syndromic and no syndromic genes identified in the American population*

Gene	Nucleotide variant	Protein variant-exon	# Families	# patients/n	Country
BBS1 (Bardet-Biedl syndrome 1)	Not reported	Not reported	1,159	1,246 (121 with RP) n=1	Brazil (8)
BBS2 (Bardet-Biedl syndrome 2)	Not reported	Not reported	1,159	1,246 (121 with RP) n=1	Brazil (8)
CDHR1 (cadherin related family member 1)	Not reported	Not reported	1,159	1,246 (121 with RP) n=1	Brazil (8)
CNGA1 (cyclic nucleotide-gated channel subunit alpha 1)	Not reported	Not reported	1,159	1,246 (121 with RP) n=1	Brazil (8)
CNGB1 (cyclic nucleotide-gated channel subunit beta 1)	Not reported	Not reported	1,159	1,246 (121 with RP) n=3	Brazil (8)
EYS (Eyes shut homolog)	Not reported	Not reported	1,159	1,246 (121 with RP) n=16	Brazil (8)
GPR98†	Not reported	Not reported	1,159	1,246 (121 with RP)	Brazil (16)

				n=1	
HGSNAT (heparan-alpha-glucosaminide N-acetyltransferase)	Not reported	Not reported	1,159	1,246 (121 with RP) n=2	Brazil (8)
RP1 (retinitis pigmentosa 1)	Not reported	Not reported	1,159	1,246 (121 with RP) n=7	Brazil (8)
DHDDS (dehydrodolichyldiphosphate synthase subunit)	Not reported	p.Lys42Glu		275, n=3	North America, Jewish ancestry (8)
MKS1 (transition zone complex subunit 1)	Not reported	Not reported	1,159	1,246 (121 with RP) n=1	Brazil (17)
PRPH2 (Peripherin 2)	Not reported	Not reported	1,159	1,246 (121 with RP) n=1	Brazil (8)
ABHD12 (Abhydrolase domain containing 12, lysophospholipase)	Not reported	Not reported	1,159	1,246 (121 with RP) n=1	Brazil (8)
MYO7A (Myosin7A)	Not reported	Not reported	1,159	1,246 (121 with RP) n=8	Brazil (8)
	c.6079_6081del	p.H2027del	1	12, n=3	Venezuela (8)
TULP1 (TUB like protein 1)	Not reported	Not reported	1,159	1,246 (121 with RP) n=1	Brazil (8)
SAG S-antigen visual arrestin	c.440G>T	p.Cys147Phe	300	12 families	North America (8)
WDR19 (WD repeat domain 19)	Not reported	Not reported	1,159	1,246 (121 with RP) n=1	Brazil (19)
	c.G3533A c.A2561C	p.R1178Q p.K854T	Not reported	35, n=1	North America (8)
CDH23(Cadherin – related 23)	c.7730_7734delTCAGT c.1624G>T	p. Phe2577Serfs∗28 p. Glu542∗	11	11	Cuba (10)
ADGRV1 (adhesion G protein-coupled receptor V1)	c.15448_15449delCT c.15448_15449delCT	p. Leu5150Hisfs∗6 p. Leu5150Hisfs∗6	11	11	Cuba (20)
PCDH15 (protocadherin related 15)	c.3661C>T	p. Gln1221∗	11	11, n= 4	Cuba (20)
RP1 retinitis pigmentosa 1	c.C1625G c.C4105T	p.S542* p.Q1369*	Not reported	35, n=1	North America, Hispanic probands (20)
ABCA4(ATP binding cassette subfamily A member 4)	c.4919G>A	p. Arg1640Gln	Not reported	143	Mexico (10)
	c.T6179G c.G6089A ()	p.L2060R p.R2030Q)	Not reported	35, n=1	North America, Hispanic probands (9)
ARL6 (ADP ribosylation factor like GTPase 6)	c.373dupA	p. Ile125AsnfsTer7	Not reported	143	Mexico (10)
PCARE (photoreceptor cilium actin regulator)	c.947delA	p. Asn316MetfsTer7	Not reported	143	Mexico (21)
CLN3 (CLN3 lysosomal/endosomaltransmembrane protein, battenin)	c.266G>A	p. Arg89Gln	Not reported	143, n=1	Mexico (9)
RDH5(Retinol dehydrogenase5)	c.839G>A	p. Arg280His	Not reported	143, n=1	Mexico (9)
RP2 (retinitis pigmentosa 2)	NC_000023.10 (NM_006915.2): c. (?_−1) _ (768+1_769−1) del (exon 1–2 deletion) c.969+2T>G		Not reported	143, n=2	Mexico (9)
RPE65 (retinoidisomerohydrolase RPE65)	c.405T>A	p. Asn135Lys	Not reported	143, n=1	Mexico (9)
SPATA7 (spermatogenesis	c.322C>T	p. Arg108Ter	Not	143, n=1	Mexico (9)

associated 7)			reported		
BBS10 (Bardet-Biedlsyndrome 10)	c.39_46delGGCGTTGC	p. Ala14GlyfsTer79 (A14Gfs*79)	1	1 n=1	Colombia (9)
GNAT1(G protein subunit alpha transducin 1)	c.282delT	p. Ala95HisfsTer9	Not reported	143, n= 1	Mexico (9)
IFT140(intraflagellar transport 140)	c.1451C>T and c.2786delC	p. Thr484Met and p. Thr929SerfsTer21	Not reported	143, n= 1	Mexico (22)
IMPG2(interphotoreceptor matrix proteoglycan 2)	c.3093_3097dupTGGAG and c.2038delG	p. glu1033ValfsTer13 and p. Glu680SerfsTer21	Not reported	143, n=1	Mexico (9)
FAM161A **FAM161 centrosomal protein A**	c.1113 C. G/+ c.1133 T. G/+ c.1153 C. G/+ c.1391 A. G/+ c.1355_6delCA/c.1355_6delCA	p. Asp371Glu/+ p. Leu378Arg/+ p. Gln385Glu/+ p. His464Arg/+ p. Thr452SerfsX3/p. Thr452SerfsX3	Not reported	273, n=4	North America (9)
USH2A (Usherina 2 A)	Not reported	Not reported	1,159	1,246 (121 with RP), n= 21	Brazil (9)
	c.2229delG	Exon 13	Not reported	37, n=7	Colombia (17)
	c.545_56del AA c.775_76delAG C.847_48el GA c.921_22dupGCCA c.1012_16delCTCT c.1256G>A (TGT>TAT) c.1679delC c.1876C>T (CGA>TGA) c.2075C>A(TGC>TGA) c.2100delG c.2276G>T(TGC>TTC) c.2299delG c.2761delC c.2898delG c.3149_50delCA c.4223C>T(CAA>TAA) c.4338_39delCT c.4510_11insA	K182fs S259fs E284fs H308fs L342fs C419F P560fs R626X C691X G700FS C759F E767fs L921fs L967fs Q1063fs Q1408X L1447fs R1504fs	Not reported	275, n=275	North America (8)
	g.129G>T c.1000CT; p.R334W c.2299delG; pE767fs polymorphisms c.504A>G; p.168T c.931A>T; p.D644V c.4252-24_13delCTTT c.4457G>A; p. R1486K		Not reported	26, n=26	Colombia (23)
	c.2299delG c.1841-2A>G	p. Glu767Serfs∗21 p. Gly614Aspfs∗6	11	11	Cuba (24)
	c.2299delG	Not reported	Not reported	40, n= 11	Cuba (23)
	c.11387C>T c.907C>A and c.5218delA c.2332G>T and c.5836 C>T	p. Pro3796Leu p. Arg303Ser and p. Ile1740PhefsTer10 p. Asp778Tyr and p. Arg1946Ter	Not reported	143, n= 4	Mexico (20)

	c.11156 G>A and c.13348 C>T	p. Arg3719His and p. Pro4450Ser			
	c.G12575A c.C13664T	p.R4192H p.P4555L	Not reported	35, n=1	North America, Hispanic probands (25)
CLRN1(Clarin 1)	c.619C>T c.619C>T	p. Arg207∗	11	11, n= 2	Cuba (10)
	Not reported	Not reported	1,159	1,246 (121 with RP), n=1	Brazil (9)
CDHR1 (cadherin related family member 1)	Not reported	Not reported	1,159	1,246 (121 with RP), n=1	Brazil (20)
	c.963G>C and c.2041−2A>C	p. Gln321His	Not reported	143, n=1	Mexico (8)
CERKL (Ceramide Kinase Like)	Not reported	Not reported	1,159	1,246 (121 with RP), n=7	Brazil (8)
	c.1633_1636dupATCA c.847C>T c.424_427delAATT and c.1032_1039dupTGGGTTCT	p. Ser546AsnfsTer21 p. Arg283Ter c.424_427delAATT p. Asn142Ter and p. Ser347LeufsTer77	Not reported	143, n=1	Mexico (9)
CRB1 (Crums cell polarity complex component 1)	Not reported	Not reported	1,159	1,246 (121 with RP), n= 5	Brazil (8)
	c.2290C>T c.1125C>G	p. Arg764Cys c.1125C>G p. Tyr375Ter	Not reported	143, n=2	Mexico (9)
MERTK (MER proto-oncogene, tyrosine kinase)	Not reported	Not reported	1,159	1,246 (121 with RP), n =6	Brazil (8)
	c.2531G>A	p. Arg844His	Not reported	143, n=1	Mexico (9)
PDE6A (Phosphodiesterase 6 A)	Not reported	Not reported	1,159	1,246 (121 with RP), n=2	Brazil (8)
	c.2302G>T c. 1705 C>A c.1684 C>T	p. Glu768Ter p. Gln569Lys p. Arg562Trp	Not reported	143, n=2	Mexico (8)
PDE6B(Phosphodiesterase 6 B)	c.703delC	p.L235Wfs*33	Not reported	35, n=1	North America, Hispanic probands (9)
RDH12(retinol dehydrogenase 12)	c.446T>C c.295C>A c.446T>C	p. Leu149Pro p. Leu99Ile p. Leu149Pro	Not reported	143, n=3	Mexico (8)
	Not reported	Not reported	1,159	1,246 (121 with RP), n=1	Brazil (9)
	c.C146A c.C295A	p.T49K p.L99I	Not reported	35, n=1	North America, Hispanic probands (10)

X-linked RP

In this review, four genes associated with xlRP were identified. RP2 and RPGR were reported in Brazil and North America, while RP3 and CHM were found only in North America. RPGR had the highest frequency of occurrence, followed by RP2 (Table 5). The syndromic and non-syndromic genes identified in the American population are listed in Table 6.

Table 5. *X-linked retinitis pigmentosa mutations in America*

Gene	Probands (n)/Country	Percentage
RPGR (retinitis pigmentosa GTPase regulator)	19 (Brazil) (8)	86.36
	N/R (North America) (26)	
	1 (North America) (10)	
	N/R (North America) (27)	
RP2 (Retinitis pigmentosa 2)	2 (Brazil) (8)	9.09
	N/R (North America) (26)	
	N/R (North America) (27)	
CHM (Rab escort protein)	1 (North America) (10)	4.55
OFD1 (RP23)	N/R (North America) (28)	0.00
	22	100

N/R: not reported

Table 6. *X-linked retinitis pigmentosa. Syndromic and no syndromic genes identified in the American population*

Gene	Nucleotide variant	Protein variant-exon	# families	# patients/n	Country
RP2 (retinitis pigmentosa 2)	Not reported	Not reported	1,159	1,246 (121 with RP), n=2	Brazil (8)
	409-411del 650-351del 515insG 670insC IVS1+3A→G 82C→G 200G→A 353G→A 565T→C	Ile37del, exon2 Phe117fsTer 155 exon 2 Ser172fsTer173, exon 2 Arg225fsTer234, exon 2 - - - Tyr27Ter, exon 1 Cys67Tyr, exon 2 ARG118His, exon 2 Leu188pro, exon 2	234	n=171	North America (26)
	c.688_692del del EX04-flanking	p. Lys230Glnfs*3 del EX04-flanking	56	n=19 Families	North America (10)
RPGR (retinitis pigmentosa GTPase regulator)	Not reported	Not reported	1,159	1,246 (121 with RP), n=19	Brazil (8)
	8C→A IVS1-15A→G 212C→T 1146T→A 1223G→T IVS10+16A→G 1333G→A 1350A→G 1354A→G 1426A→G IVS12-101t→A IVS12-100 1-bpins IVS12-97T→C	Promoter Intron 1 Exon 3 Exon 10 Exon 10 Intron 10 Exon 11 Exon 11 Exon 11 Exon 11 Intron 12 Intron 12 Intron 12 Intron 12	234	n=185	North America (26)

	IVS12-93 2-bpins IVS12+11A→G 1635-1637del 1657C→T 1746G→A IVS16-137T→A IVS17+46C→T IVS18-11T→C	Intron 13 Exon 14 Exon 14 Exon 14 Intron 16 Intron 17 Intron18			
	c.2333delA	p.E778Pfs*83	Not reported	35, n=1	North America, Hispanic probands (27)
	c.194G > A c.297_306del c.865A > G c.934þ1G > T c.1377_1378del c.1573-8A > G c.1636G > T c.2188G > T c.2212G > T c.2218G > T c.2340del c.2405_2406del c.2442_2445del c.2517_2518del c.2625dupA c.2763_2764del c.3106del	p. Gly65Asp p. Leu100Glnfs*30 p. Ile289Val Splicing p. Leu460Ilefs*2 Splicing p. Glu546X p. Gly730X p. Gly738X p. Glu740X p. Ala781Argfs*34 p. Glu802Glyfs*32 p. Gly817Lysfs*2 p. Glu841Glyfs*237 p. Gly876Argfs*203 p.Glu922Glyfs*156 p.Glu1036Lysfs*53	56	n=19 Families	North America (10)
CHM Rab escort protein	c.116+1G>A	(p.?)	Not reported	35, n=1	North America, Hispanic probands (28)

Simple forms of RP

A total of 21 studies conducted in Mexico and North America reported 14 gene mutations linked to sporadic cases of RP. In cases with undetermined inheritance patterns, USH2A and RPE65 were the most frequently identified genes. ABCA4, RP1, RDH12, RPE65, and USH2A were associated with arRP, SNRP200 with adRP, and RPGR with xlRP in the Mexican population (Table 7). A complete list of syndromic and non-syndromic genes identified in the American population is provided in Table 8.

Table 7. *Mutations for sporadic cases in America*

Gene	Probands (n)/Country	Percentage
USH2A (Usherin 2 A)	1 (Mexico) (9)	4.76
	3 (North America) (10)	14.29
RPE 65 (retinoidisomerohydrolase RPE65)	3 (Mexico) (9)	14.29
ABCA4 (ATP binding cassette subfamily A member 4)	1 (Mexico) (9)	4.76
CFAP410 (cilia and flagella associated protein 410)	1 (North America) (10)	4.76
CERKL (Ceramide Kinase Like)	1 (Mexico) (9)	4.76
IDH3B (isocitrate dehydrogenase (NAD (+)) 3 non-catalytic subunit betas)	1 (Mexico) (9)	4.76
IFT140 (intraflagellar transport 140)	1 (Mexico) (9)	4.76
RDH12 (Retinoldehydrogenase 12)	2 (Mexico) (9)	9.52
RHO (Rhodopsin)	1 (North America) (10)	4.76
RP1 (Retinitis pigmentosa1)	1 (Mexico) (9)	4.76
RPGR (retinitispigmentosa GTPase regulator)	1 (Mexico) (9)	4.76
	1 (North America) (10)	4.76
PRPF8 (pre-mRNA processing factor 8)	1 (North America) (10)	4.76
PDE6B (Phosphodiesterase 6 B)	1 (North America) (10)	4.76
SNRNP200 (Putative U5 small nuclear ribonucleoprotein 200 kDa helicase)	1 (Mexico) (9)	4.76
	21	100.00

N/R: not reported

Table 8. *Simple retinitis pigmentosa. Syndromic and no syndromic genes identified in the American population*

Gene	Nucleotide variant	Protein variant-exon	# families	# patients/n	Country
ABCA4 (ATP binding cassette subfamily A member 4)	c.1417_1420dupATTA and c.5196+1G>A	p. Thr474AsnfsTer4	Not reported	143, n=1	Mexico (9)
CFAP410(cilia and flagella associated protein 410)	c.G218C c.G364C	p.R73P p.D122H	Not reported	35, n=1	North America, Hispanic probands (10)
CERKL (Ceramide Kinase Like)	c.847C>T	p. Arg283Ter	Not reported	143, n=1	Mexico (9)
IDH3B (isocitrate dehydrogenase (NAD (+)) 3 non-catalytic subunit betas)	c.857G>A	p. Gly286Glu	Not reported	143, n=1	Mexico (9)
IFT140 (intraflagellar transport 140)	c.386T>G c.1377G>A	p. Leu129Trp p. Trp459Ter	Not reported	143, n=1	Mexico (10)
RDH12 (retinol dehydrogenase 12)	c.295C>A c.295C>A and c.697G>C	p. Leu99Ile p. Leu99Ile and p. Val233Leu	Not reported	143, n=2	Mexico (9)
RHO (Rodopsin)	c.C408A	p.Y136*	Not reported	35, n=1	North America, Hispanic probands (9)

RP1 (retinitis pigmentosa1)	c.3150delA	p. Lys1050AsnfsTer7	Not reported	143, n=1	Mexico (9)
RPE 65 (retinoid isomerohydrolase RPE65)	c.131G>A and c.61delG c.386 C>T and c.1067dupA c.95−2A>T	p. Arg44Gln and p. Glu21AsnfsTer10 p. Thr129Ile and p. Asn356LysfsTer9 Not reported	Not reported	143, n=3	Mexico (9)
RPGR (retinitis pigmentosa GTPase regulator)	c.1859_1860delAG	p. Lys620ArgfsTer9	Not reported	143, n=1	Mexico (10)
	c.G494A	p. G165D	Not reported	35, n=1	North America, Hispanic probands (9)
PRPF8 (pre-mRNA processing factor 8)	c.C5041T	p. R1681W	Not reported	35, n=1	North America, Hispanic probands (9)
PDE6B (Phosphodiesterase6 B)	c.G704C ()	p. R235P	Not reported	35, n=1	North America, Hispanic probands (10)
USH2A (Usherin 2 A)	c.12575G>A and c.3629T>C	p. Arg4192His and p. Leu1210Pro	Not reported	143, n=1	Mexico (10)
	c.G12575A c.T9799C c.1841-2A>G c.G8254A c.T12443C	p.R4192H p.C3267R (p.?) p.G2752R p. L4148P	Not reported	35, n=3	North America, Hispanic probands (10)
SNRNP200 (Putative U5 small nuclear ribonucleoprotein 200 kDa helicase)	c.3260C>T	p. Ser1087Leu	Not reported	143, n=1	Mexico (9)

DISCUSSION

RP is the most prevalent form of retinal dystrophy (3, 29, 30) and is characterized by significant genetic heterogeneity. Mutations in the same gene can lead to varying clinical presentations across different individuals (31). Additionally, the frequency of specific RP-related mutations varies between populations (32).

This review of RP genetic characterization in American populations identified Brazil as the country with the highest number of reported genes, while most of the included publications originated from North America. The arRP had the largest number of associated genes reported, followed by adRP, and then sporadic (simple) RP. In contrast, only three genes were identified in association with xlRP.

Among RP subtypes, adRP generally has a more favorable prognosis compared to others (32). In this review, the RHO and PRPF31 genes were found in four and three American countries, respectively. Mutations in PRPF31 were also reported as the third most common cause of adRP in several countries, including China, France, India, Japan, and the USA. Similarly, mutations in RHO, PRPF31, and RP1 were documented in both Indian and Belgian populations (33-35).

Although new mutations and genes associated with RP subtypes continue to be discovered each year through ongoing research (3), RHO mutations remain significant—accounting for approximately 30% of cases in Americans of European descent and 10% in Chinese patients (32). Additionally, RHO mutations have been reported in individuals from Israel, Palestine (36), Spain (37), Korea (38), Sweden, and Iran. A study on adRP in Italian families, consistent with this review's findings, identified RHO as the most frequently involved gene, with mutations found in 16% of the families. The second most commonly implicated gene in Italy was RP1, whereas PRPF31 mutations were not reported in that cohort (39). Similarly, a study from France found RHO and PRPH2 to be the most frequent genes involved in

adRP, while PRPF31 and RP1 were less commonly reported (40).

There are an estimated 55 genes believed to contribute to arRP, accounting for about 2–5% of all RP cases (40, 41). USH2A mutations are a major cause of non-syndromic arRP globally. This review identified five countries with the highest occurrence of USH2A, which is also recognized as the leading genetic cause of the Usher syndrome—a condition that affects both vision and the auditory–vestibular system (3, 42). In Brazil, USH2A and MYO7A were the most commonly identified genes among RP patients (8). Another relevant gene is ABCA4, reported in both Brazil and North America. While primarily associated with inherited retinal dystrophies distinct from RP, ABCA4 mutations are commonly found in patients with Stargardt disease and, to a lesser extent, in cone-rod dystrophy and RP cases (43).

A study conducted in the Jerusalem region, known for its high consanguinity rate, found that 63% of cases had an arRP inheritance pattern, particularly in the Arab Muslim cohort. The most frequently identified genes were DHDDS, FAM161A, and EYS (44). These results differ from those of this review, where USH2A is the primary cause of RP in arRP cases.

In a study of a four-generation British family with adRP, mutations in the RDH12 gene were detected. In the USA, this gene was associated with arRP and sporadic RP cases (45). In a Japanese cohort, EYS was identified as the most common gene, affecting 44.5% of diagnosed patients, which contrasts with the findings in this review (46).

A longitudinal study in France, spanning 21 years, examined 21 families (33.3%) and found mutations in both alleles for MERTK, RDH12, RP1, RPE65, ABCA4, PDE6A, and CNGB1, while nine families had a single heterozygous mutation in USH2A, BBS1, LRAT, and RPE65 (47). These results differ from the most common genes identified in this review.

A study on IRDs in France, where RP was the most common, found mutations for xlRP in RP2 (7.7%), RPGR (76.9%), and unidentified mutations (15.4%) (47). Six loci were implicated in xlRP, the most severe form of RP. As observed in this review, RPGR and RP2 are the main genes associated with xlRP (found in 70–90% and 6–20% of cases, respectively). These mutations also cause xlRP in the Japanese population, with significant visual impairment (48). RPGR mutations are present in 30% of Americans of European descent and 10% of Chinese patients (5, 32). Additionally, in 30–60% of xlRP cases, 17 mutations in the ORF15 region of RPGR were implicated (41).

Table 9. *Functions of genes associated with adRP, arRP, xlRP, and simplex RP*

Inheritance pattern	Gene	Function
Autosomal dominant	*RHO*	Light absorption (50)
	PRPF31	RNA splicing (51)
Autosomal recessive	*USH2A*	Development and maintenance of cells of the inner ear and retina (52)
	EYS	Maintenance of the integrity and protein trafficking of photoreceptor cells (52)
	MYO7A	Renewal of the outer photoreceptor disc, distribution, and migration of Retinal pigment epithelial melanosomes and phagosomes, regulation of opsin transport (51)
X-linked	*RPGR*	Exact function unknown (53)
	RP2	Maintenance of Golgi cohesion and targeting of proteins to the plasma membrane (54)
Simplex	*USH2A*	Development and maintenance of cells of the inner ear and retina (52)
	RPE65	Regeneration of the visual pigment necessary for both rod and cone-mediated vision (55)
	RDH12	Part of the visual cycle, reduction of all-trans and all-cisretinoids (56)

adRP: Autosomal dominant retinitis pigmentosa, arRP: Autosomal recessive retinitis pigmentosa, xlRP: X-linked retinitis pigmentosa, and simple retinitis pigmentosa

Simplex or isolated cases refer to patients who do not have affected first-degree relatives and no reports of more distant family members being affected. For these cases, USH2A and RPE65 were identified as the most common causative genes for RP. This aligns with a study on Spanish families, where USH2A was found to be more prevalent; however, no mention of RPE65 mutations was made (49). Table 9 summarizes the main physiological functions that may be affected by gene mutations and lists the most frequently implicated causative genes associated with the different inheritance patterns of RP.

Finally, several patient organizations exist in the region, with some of the most well-known being Alianza de Retinosis Pigmentaria Argentina (ARPA), Fundación Argentina de Retinosis Pigmentaria (FARPA) (https://retinosis.org/fundacion-argentina-de-retinosis-pigmentaria), Asociación Colombiana de RP (ACORP), Asociación Retina Brasil, Asociación Retina Sao Paulo (http://retinaiberoamerica.org/retina-sao-paulo), undación Lucha contra la Retinosis Pigmentaria in Chile (FUNDALURP) (http://fundalurp.cl), Fundación Retina República Dominicana, Fundación de Retinitis Pigmentosa in Puerto Rico (https://retinitispigmentosapr.com), and Asociación Nacional de Retinosis pigmentaria in Mexico (https://www.facebook.com/retinosispigmentariamexico). These organizations are part of Retina Iberoamerica and Retina Internacional. They work to improve patient access to research, facilitate participation in controlled clinical trials worldwide, and provide emotional support and basic information about the disease (56).

The main limitation of this review was the lack of available literature from all American countries, particularly from Latin America. Additionally, some studies reported the presence of gene mutations but did not specify the number of affected probands.

CONCLUSION

Most of the genes currently identified as causing RP worldwide are also present in America. In the American population, the most common genes associated with adRP are RHO, PRPF31, and SNRPN200. The most frequent genes linked to arRP are USH2A, EYS, and MYO7A; for xlRP, RPGR and RP2 are implicated, while in simplex forms, USH2A, RPE65, and RDH12 are the primary genes involved.

There are similarities in the genetic characterization of RP between America and European countries, particularly for adRP and xlRP, although there are notable differences when compared to Asian populations, which show a greater variety in the presentation of gene mutations.

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Competing interests

Authors declare no conflicts of interest.

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Geni povezani sa retinitisom pigmentozom u populaciji Amerike: sistematski pregled

Olivia Margarita Narváez[1], Hugo Mendieta Zerón[2], Orlando Torres[3], Magally Escobar[4], Martha Liliana Trujillo-Güiza[4]

[1]*Univerzitet „Santo Tomás", Fakultet za optometriju, Bukaramanga, Kolumbija*
[2]*Autonomni univerzitet savezne države Meksiko (UAEMex) i Bolnica za majku i perinatalnu negu „Mónica Pretelini Sáenz", Medicinski fakultet, Toluka, Meksiko*
[3]*Univerzitet „Antonio Nariño", Fakultet veterinarske medicine, Bogota, Kolumbija*
[4]*Univerzitet „Antonio Nariño", Medicinski fakultet, Bogota, Kolumbija*

SAŽETAK

Uvod/Cilj. Retinitis pigmentoza (RP) predstavlja heterogenu grupu naslednih bolesti mrežnjače, koje karakteriše postepena degeneracija štapičastih i kupastih foto-receptora. Bolest se primarno nasleđuje, a u njenoj patogenezi učestvuje velik broj različitih genskih mutacija. Cilj ovog istraživanja bio je da sumira rezultate studija koje su ispitivale gene povezane sa retinitisom pigmentozom kod bolesnika sa autozomno dominantnim (adRP), autozomno recesivnim (arRP) i X-vezanim (xlRP) obrascem nasleđivanja na području Amerike.

Materijal i metode. Sprovedena je sveobuhvatna pretraga literature u bazama podataka *Medline*/*PubMed, SciELO, Redalyc, ScienceDirect* i *Google Scholar* (na engleskom i španskom jeziku). U pregledu je analizirano sedamdeset pet radova objavljenih između 2010. i 2020. godine, a u finalnu analizu uključena je dvadeset jedna studija.

Rezultati. Najčešće mutacije gena identifikovane kod bolesnika sa adRP-om u Americi bile su RHO (rodopsin) i PRPF31 (faktor prerade pre-mRNK 31), a kod bolesnika sa arRP-om USH2A (ušerin 2A) i EYS (homolog proteina „zatvorenih očiju"). Mutacije gena RPGR (regulator GTP-aze za retinitis pigmentozu) i RP2 (retinitis pigmentoza 2) bile su dominantne kod bolesnika koji su imali xlRP.

Zaključak. Većina gena koji su širom sveta identifikovani kao uzročnici RP-a pronađena je i kod bolesnika u Americi, s tim što su uočene određene sličnosti i razlike u poređenju sa populacijom u Aziji i Evropi.

Ključne reči: **autozomno dominantno, autozomno recesivno, obrazac nasleđivanja, retinitis pigmentoza, X-vezano nasleđivanje**