November 2017

Retinitis pigmentosa genes implicated in South Asian populations: a systematic review

Sidra Zafar
Aga Khan University

Khabir Ahmed
Aga Khan University, khabir.ahmed@aku.edu

Azam Ali
Aga Khan University, azam.ali@aku.edu

Rashid Baig
Aga Khan University, rashid.baig@aku.edu

SYSTEMATIC REVIEW

Retinitis pigmentosa genes implicated in South Asian populations: a systematic review

Sidra Zafar, Khabir Ahmad, Azam Ali, Rashid Baig

Abstract

Retinitis pigmentosais one of the most prevalent causes of inherited retinal dystrophies worldwide. The widespread custom of consanguineous marriages in South Asian countries puts the population at risk for autosomal recessive disorders including retinitis pigmentosa.

This systematic review was done between May and December 2015.A comprehensive literature search was carried out using MEDLINE and CINAHL databases and all relevant articles on causative mutations for non-syndromic Retinitis pigmentosa from 1999 till 2015 were included. Overall, 41 articles were identified involving 66 families; 28(68%)from Pakistan, 12(29%) from India and 1(2.4%) from Bangladesh. No data was available from the rest of countries in the region. Autosomal recessive was the most common pattern of inheritance and out of the known 60 genes thought to be involved in the pathogenesis of non-syndromic Retinitis pigmentosa, 32(53%) were identified in South Asia. Although significant progress has been made in this regard, there are many more loci that are yet to be identified. Our study found that significant gaps in knowledge exist due to lack of reported literature from countries other than Pakistan and India and the absence of cost-effective screening programmes in place.

Keywords: Retinitis pigmentosa, Genes, South Asia.

Background

Retinitis pigmentosa (RP) is one of the most common hereditary retinal dystrophies worldwide, with a prevalence of approximately 1 in 5000 to 1 in 1000.[1-3] It is characterised by progressive degeneration of the photoreceptors (rods and cones) which manifests as night blindness and loss of peripheral visual fields initially and partial or complete blindness in later, more advanced stages. On clinical examination, changes in the affected retina include a pale optic disc, attenuated vasculature, pigmentary deposits appearing as bony spicules, atrophic retinal tissue and an abnormal electroretinogram (ERG) response. RP may be inherited in an autosomal dominant (adRP), autosomal recessive (arRP) or an X-linked recessive pattern. Less commonly, it may be seen as a digenic or a mitochondrial trait. AdRP represents 15-20% of all cases of RP, arRP comprises 20-25% of cases and the X-linked recessive type makes up 10-15% of cases. The remaining 40-55% of cases are sporadic but many of these are presumed to be arRP.[1,2,4-6]

In addition to simple RP, syndromic forms of the disease involving multiple organs also exist. The most frequent form of syndromic RP, is Usher syndrome (US). It is characterised by early-onset or congenital sensorineural hearing loss (SNHL) followed by development of RP.[7] Bardet-Biedl syndrome (BBS), the second most common form includes RP, polydactyly, obesity, renal abnormalities and mental retardation.[8]

Major progress has been made in the past few decades in identifying genes and mutations causing inherited retinal dystrophies. The various techniques for identification of genetic mutations have included linkage mapping and homozygosity mapping. Once mapped, the underlying gene can be found by various targeted sequencing strategies.

Mutations in more than 60 genes (see RetNet) are currently known to be associated with non-syndromic RP alone. These include genes encoding components of the photo transduction cascade, proteins involved in retinoid metabolism, cell-cell interaction proteins, photoreceptor structural proteins, transcription factors, intracellular transport proteins and splicing factors.[5,9] Although there have been reports identifying RP mutations in different South Asian populations, but this information has not been systematically reviewed and much work is still required for the discovery of all of the causative genes.[10]

Understanding this complex disease at the molecular level along with clinical testing will not only help diagnose affected individuals and families at an earlier stage, but can eventually lead to treatment and prevention. In this systematic review, we planned to study RP genes and mutations reported in South Asian populations and see any overlapping genetic mutations that might exist.

Aga Khan University, Karachi.
Correspondence: Sidra Zafar. Email: sidrazafariqbal@gmail.com

Methods

This systematic review was carried out between May and December 2015. All studies published between 1999 and 2015 identifying RP genetic mutations in South Asian populations were eligible to be included. We searched the MEDLINE and CINAHL databases for relevant articles. Search terms used were 'retinitis pigmentosa', 'RP', 'non-syndromic RP', 'genes', 'mutations', 'South Asia', 'Asia' and names of all the countries in this region; Afghanistan, Bhutan, Bangladesh, India, Myanmar, Nepal and Pakistan. Irrelevant articles not meeting the inclusion criteria, evident from the titles and abstracts, were excluded. Relevant articles referenced in publications were obtained and the references of identified studies were also searched to identify any additional articles that might have been missed. No language restriction was applied. A descriptive analysis of all data was carried out and the results were expressed in frequencies and/or percentages.

Results

A total of 148articles were identified from the literature search, all but 41(27.7%) were excluded after reading their abstracts or full text (Figure). These articles involved 66 families. Of the included articles, 28(68%) were from Pakistan,

Table: Identified Retinitis pigmentosa genetic mutations in South Asia.

Gene	Nucleotide variant	Protein variant	Phenotype	# Families	# Patients	Country	References
ABCA4	c.6658C>T	p.(Gln2220*)	arRP	1	6	Pakistan	(20)
BEST1	c.418C>G	p.(Leu140Val)	arRP	1	4	Pakistan	(21)
C8orf37	c.224-2A>C	p.(?)	arRP	1	2	Pakistan	(13)
C8orf37	c555G>A	p.W185	arRP	1	3	Pakistan	(3)
CC2D2A		p.(V728EfsX741)	arRP w/ MR	1	3	Pakistan	(22)
CERKL	c.316C>A	p.(Arg106Ser)	arRP	1	3	Pakistan	(23)
CERKL	c.847C>T	p.(Arg283*)	arRP	1	6	Pakistan	(1)
CLRN1	c.92C>T	p.(Pro31Leu)	arRP	1	6	Pakistan	(24)
CNGA1	c.626_627del	p.(Ile209Serfs*26)	arRP	1	7	Pakistan	(25)
CNGA1	c.1298G>A	p.(Gly433Asp)	arRP	1	3	Pakistan	(26)
CNGB1	c.412-1G>A	p.(?)	arRP	1	10	Pakistan	(16)
CNGB1	c.2284C>T	p.(Arg762Cys)	arRP	1	5	Pakistan	(9)
CNGB1	c.2493-2A>G	P. (?)	arRP	1	10	Pakistan	(26)
CRB1	c.2536G>A	p.(Gly846Arg)	arRP	1	6	Pakistan	(27)
CRB1	c.3101T>C	p.(Leu989Thr)		1		Pakistan	(7)
CRB1	c.3347T>C	p.(Leu1071Pro)	arRP	1	7	Pakistan	(27)
CRB1	c.3343_3352del	p.(Gly1115Ilefs*23)	arRP	1	9	Pakistan	(28)
CRB1	c.2234C>T	p.(Thr745Met)	arRP	1	2	Pakistan	(8)
DHX38	c.995G>A	p.(Gly332Asp)	arRP w/ macular coloboma	1	4	Pakistan	(29)
EYS	c.8299G>T	p.(Asp2767Tyr)	arRP	1	7	Pakistan	(30)
IMPG2	c.1680T>A	p.(Tyr560*)	arRP	1	2	Pakistan	(31, 32)
MERTK	c.7186->T	p.(?)	arRP	1	3	Pakistan	(33)
PDE6A	c.889C>T	p.(Gly297Ser)	arRP	1	4	Pakistan	(34)
PDE6A	c.1264-2A>G	p.(?)	arRP	1	5	Pakistan	(34)
PDE6A	c.2218_2219insT	p.(Ala740Valfs*2)	arRP	1	3	Pakistan	(34)
PDE6B	c.1160C>T	p.(Pro387Leu)	arRP	1	6	Pakistan	(34, 35)
PDE6B	c.1655G>A	p.(Arg552Gln)	arRP	1	9	Pakistan	(35)
PDE6B	c.1722+1G>A	p.(?)	arRP	1	4	Pakistan	(9)
PROM1	c.1726C>T	p.(Gln576*)	arRP	1	6	Pakistan	(36)
RHO	c.448G>A	p.(Glu150Lys)	arRP	2	6	Pakistan	(15, 36)
RP1	c.1458_1461dup	p.(Glu488*)	arRP	2	9	Pakistan	(15, 37, 38)
RP1	c.4555del	p.(Arg1519Glufs*2)	arRP	1	5	Pakistan	(37, 38)
RP1	c.5252del	p.(Asn1751Ilefs*4)	arRP	1	4	Pakistan	(37)
SPATA7	c.253C>T	p.(Arg85*)	arRP/arLCA	2	3	Pakistan	(37, 39)
TTC8	c.115-2A>G	p.(?)	arRP	1	4	Pakistan	(39, 40)
TULP1	c.1138A>G	p.Thr380Ala	arRP	3	34	Pakistan	(26, 40-42)
TULP1	c.1445G>A	p.(Arg482Gln)	arRP	1	8	Pakistan	(26, 41, 42)
TULP1	c.1466A>G	p.(Lys489Arg)	arRP	4	19	Pakistan	(41, 42)
ZNF13	c.1015T>C	p.(Cys339Arg)	arRP	1	4	Pakistan	(6, 9, 42)

Contd. on next page>>>

ABCA4	c.1995C>A	Tyr665X	arRP	1	2	India	(6, 9, 43)
ABCA4	c.42566T>C	Met1419Thr	arRP	1	2	India	(43)
CRB1	c.2715G>A	Arg905Arg	arRP	1	2	India	(43)
FAM161A	c.685C>T	p.(Arg229X)	arRP	1	4	India	(43-46)
MERTK	c.721C>T	p.(Gln 241*)	arRP	1	3	India	(44-47)
MRP3	c.498delC	p.(166ProfsX26)	arRP	1	3	India	(1, 47)
NR2E3	c.143_144delGCins25	p.(48fs*)	arRP	3	2	India	(1)
PRPF31	c.358_359 del AA	p.(Lys120GlufsX122)	Sporadic	N/A	1	India	(1, 48)
PRPF31	c.358_359 del AA	IVS6+1G/A	adRP	1	2	India	(48)
PRPF31	c.59_65del7	p.(Gly20AlafsX43)	adRP	1	14	India	(48, 49)
RHO	c.316G/A	p.(Gly106Arg)	Sporadic	N/A	1	India	(48, 49)
RHO	c.345G>A		Sporadic	N/A	1	India	(48, 50)
RHO	c.345G>A	p.Gly106Arg	adRP	1	3	India	(50)
RLBP1	c.451C>T	p.(Arg151Trp)	arRP	1	2	India	(43, 50)
RP1	c.2847delT	p.(Asn949LysfsX32)	arRP	1	2	India	(43)
RP63	c.(?)	p.(?)	adRP	1	14	India	(43, 51)
RPE65	c.1060delA	p.(Asn356MetfsX16)	arRP	1	2	India	(43, 51)
RPE65	c.321T>G	p.(Arg1017Lys)	arRP/LCA	N/A	1	India	(43, 52)
SPATA7	c.544delC	p.(Gln181fs)	arRP	1	2	India	(52, 53)
TULP1	c.1047T>G	p.(Asn349Lys)	arRP	1	2	India	(43, 53)
TULP1	1199G>A	p.(Arg400Gln)	arRP	1	2	India	(1, 43)
PRCD	c.5G>A	p.C2Y	sporadic	N/A	1	Bangladesh	(1, 54)

The identified mutations within genes, the mode of inheritance, the number of the families identified with those mutations and the countries in which they were identified.

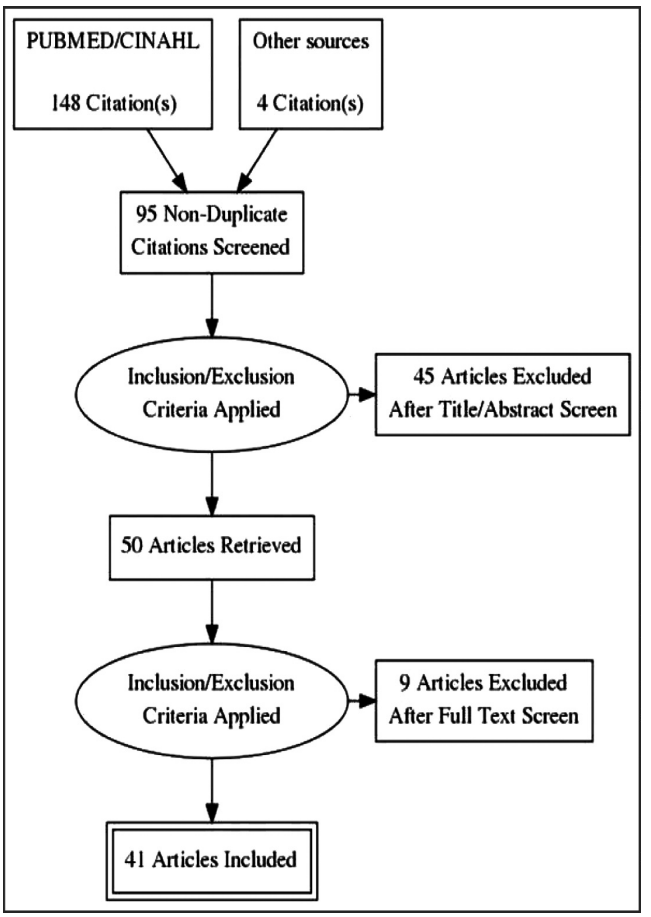

Figure: Flow chart representing literature search.

12(29%) from India and 1(2.4%) from Bangladesh. Autosomal recessive pattern of inheritance was identified in 57(88%) of the families, while 5(6.8%) and 4(5.6%) were autosomal dominant and sporadic mutations, respectively. Mutations in ABCA4, CRB1, RHO, SPATA7 and TULP1 were seen to overlap in both Pakistani and Indian populations. C8orf37 was identified in two families of Pakistani origin. CRB1, PDE6A/B, RP1 and TULP1 were found to be more commonly mutated in families of Pakistani origin. In India, mutations in PRPF31, RHO and TULP1 were more common (Table).

Discussion

After extensive review of literature on RP in South Asian populations, we found that more than half of the genes currently known to cause non-syndromic RP were present in this part of the world. The studies were mainly from Pakistan (Punjab province) and southern India. Autosomal recessive (AR) inheritance pattern was the most common (95%). This could be explained by the high rate of consanguineous marriages among South Asian families. Previous studies have shown consanguineous marriages to account for 20% to 59% of the total marriages in India and Pakistan; mainly involving first-cousin marriages.[11,12] The high rate of consanguinity also makes South Asian populations suitable for identification of genetic mutations through homozygosity mapping. In fact, BEST1, CC2D2A, IMPG2, ZNF513, CNGA1 AND PRCD were among the retinal genes first identified through genetic studies of South Asian families. Similarly, as also mentioned by Khan et al, TTC8, CLRN1 and RHO that were

first identified as causative genes for syndromic and adRP respectively, are now known to result in arRP as well.

C8orf37 is one the more recently implicated genes in RP and accounts for less than 0.4% of all cases. It was identified in two families of Pakistani origin. Both families had a history of consanguinity and, interestingly, one of the two families was settled in the United Kingdom, providing further implication of consanguinity as being responsible for homozygous mutations in affected individuals and an autosomal recessive inheritance for RP.[13]

RP is considered to be one of the most common causes of hereditary childhood blindness in South Asia. A study showed the prevalence of RP to be as high as 1 in 372 in rural areas of southern India and approximately 20% of childhood blindness in Pakistan is attributed to RP.[14]

Studies have shown that population structure, ethnicity and ancestry may have a role in determining genetics of diseases. Azam et al. discovered a c.448G>A mutation in RHO to cause arRP in three ethnically variable and geographically isolated families of Pakistani and Indian origins. Haplotype analysis by the authors was suggestive of a common ancestry though the families had been living in their present locations without any sort of contact between them for decades. This goes on to demonstrate that the effect of common ancestry may be preserved for a significant period of time.[15]

Furthermore, understanding the disease at the molecular level will not only lead to better diagnostic and novel therapeutic modalities, but is important from a genetic counselling standpoint as well. Consanguineous marriages represent a major risk factor for autosomal recessive diseases, including RP. Families have little knowledge of the inheritance of these diseases and there are no screening programmes in place. Therefore, it is imperative that in countries where consanguineous marriages are so commonly practised, national educational programmes be set up to create awareness regarding the lifelong implications the disease might have on one's quality of life along with cost-effective screening programmes. This will also have a positive influence of reducing burden of disease.

Mutations in TULP 1, CRB 1 and PRPF31 have been found to be more commonly mutated in both Indian and Pakistani populations. Worldwide prevalence of arRP-associated mutations is reported as; USH2A (12%) ABCA4 (8%), PDE6B (7%), CNGB1 (6%), and PDE6A(5%).USH2A mutations are most frequently associated with the arRP variant (c.2299del; p. (E767fs)). However, its most commonly mutant variantis almost always found in a heterozygous state, possibly precluding its detection by homozygosity mapping.[16]

In a recent study of 436 Israeli persons with non-syndromic RP (mainly arRP or sporadic), the most frequently mutated genes were DHDDS, FAM161A, and EYS, different from mutations that we found in our study population.[17] In another study that looked at 150 Saudi Arabian families affected with RP, the identified mutations included RP1, TULP1, RPGRIP1, and CRB1. These genetic mutations were more similar to our South Asian study sample.[18] Interestingly, widespread beliefs of common ancestry with Arabs exist among different South Asian populations. The validity to these claims can be determined through genetic analysis data. There was, in fact, a published article that showed a subset of lineages originally from Pakistan and India to actually have a significantly greater genetic affinity to Arab populations than do their neighbouring populations from India and Pakistan. The Indian subcontinent was central to Arab trading routes dating as far back as the 14th-16th centuries, which can in part explain the high genetic inflow in this region compared to other parts of the world.[19] Studying genetic similarities and differences of RP in various populations can therefore be of immense importance for identification of relationship between genotype and phenotype, and genotype and environment, and, more interestingly, why, if certain populations are at an increased risk.

The included studies were uniform in their definition and diagnosis of RP. Diagnosis of affected individuals was based on clinical and electrophysiological grounds. Methods employed for identification of implicated genetic mutations conformed to international standards. Another important strength was the use of screening for the identified genetic mutations in ethnically-related controls.

Limitations of our review article are, firstly, lack of literature available from other South Asian countries. The included studies originated mainly from India and Pakistan and only a single study from Bangladesh could be included. Therefore, we are not aware about the prevalence of RP in those nations and how the disease genotype and phenotype here compares with the rest of the world.

Furthermore, sufficient government support networks seem to be lacking for RP patients and their families. Visual loss has substantial impact on quality of life and causes significant financial burden for the patients and their families. This highlights the need for establishing specialised RP-referral areas where services like cost-effective screening, visual rehabilitation and interventions to slow progression of visual acuity and genetic and psychological counselling can be provided. However, further research is needed to develop

effective service models and identify health policies that can cater to greater populations with visual loss.

We believe that our work has helped organise existing genetic data and has also identified where gaps in knowledge exist. The results of our review can serve as a platform for formulating RP-centred health policies and in encouraging the involved countries towards maintaining an epidemiological register. RP remains one of the most common causes of blindness in children and adults and it would definitely be worthwhile studying and comparing information from all the different regions which will assist in developing effective prevention and therapeutic strategies.

Conclusions

More than half of the genes associated with non-syndromic RP were found to be present in South Asia. The high rate of consanguinity makes South Asia an ideal study population and while significant progress has been made in identification of RP associated genetic mutations, genetic epidemiology still remains a challenging issue. There has been little or no attention to the link between certain genetic mutations and ethnicity or a number of other factors. Our review found the data to be deeply uneven, focussing only on some of the regions in India and Pakistan to the exclusion of populous countries like Bangladesh. Efforts need to be stepped up for rapid discovery of the remaining genes and such an endeavour would require a well-knit association between the involved state health departments, specialist ophthalmologists and geneticists/epidemiologists. This is a matter of utmost importance because even though RP has known to exist since the 1850s, we are still without a significant breakthrough in terms of its cure.

Disclaimer: The study was registered with PROSPERO.

Conflict of Interest: None.

Source of Funding: None.

References

1. Kannabiran C, Singh H, Sahini N, Jalali S, Mohan G. Mutations in TULP1, NR2E3, and MFRP genes in Indian families with autosomal recessive retinitis pigmentosa. Mol Vis. 2012;18:1165-74.
2. Dandona L, Dandona R, Srinivas M, Giridhar P, Vilas K, Prasad MN, et al. Blindness in the Indian state of Andhra Pradesh. Invest ophthalmol Vis Sci. 2001;42:908-16.
3. Parmeggiani F. Clinics, Epidemiology and Genetics of Retinitis Pigmentosa. Curr Genomics. 2011; 12:236-7.
4. Bundey S, Crews SJ. A study of retinitis pigmentosa in the City of Birmingham. I Prevalence. J Med Genet. 1984; 21:417-20.
5. Maubaret C, Hamel C. [Genetics of retinitis pigmentosa: metabolic classification and phenotype/genotype correlations]. J Fr Ophtalmol. 2005; 28:71-92.
6. Li L, Nakaya N, Chavali VR, Ma Z, Jiao X, Sieving PA, et al. A mutation in ZNF513, a putative regulator of photoreceptor development, causes autosomal-recessive retinitis pigmentosa. Am J Hum Genet. 2010;87:400-9.
7. Ahmed ZM, Riazuddin S, Bernstein SL, Ahmed Z, Khan S, Griffith AJ, et al. Mutations of the protocadherin gene PCDH15 cause Usher syndrome type 1F. Am J Hum Genet. 2001;69:25-34.
8. Ajmal M, Khan MI, Neveling K, Tayyab A, Jaffar S, Sadeque A, et al. Exome sequencing identifies a novel and a recurrent BBS1 mutation in Pakistani families with Bardet-Biedl syndrome. Mol Vis. 2013;19:644-53.
9. Naz S, Riazuddin SA, Li L, Shahid M, Kousar S, Sieving PA, et al. A novel locus for autosomal recessive retinitis pigmentosa in a consanguineous Pakistani family maps to chromosome 2p. Am J Ophthalmol. 2010;149:861-6.
10. Singh HP, Jalali S, Narayanan R, Kannabiran C. Genetic analysis of Indian families with autosomal recessive retinitis pigmentosa by homozygosity screening. Invest ophthalmol Vis Sci. 2009;50:4065-71.
11. Krishnaiah S, Subba Rao B, Lakshmi Narasamma K, Amit G. A survey of severe visual impairment in children attending schools for the blind in a coastal district of Andhra Pradesh in South India. Eye (Lond). 2012; 26:1065-70.
12. Yunis K, Rafei RE, Mumtaz G. International Perspectives. Consanguinity: Perinatal Outcomes and Prevention - A View from the Middle East. 2008;9:e59-e65.
13. Ravesh Z, El Asrag ME, Weisschuh N, McKibbin M, Reuter P, Watson CM, et al. Novel C8orf37 mutations cause retinitis pigmentosa in consanguineous families of Pakistani origin. Mol Vis. 2015;21:236-43.
14. Sen P, Bhargava A, George R, Ve Ramesh S, Hemamalini A, Prema R, et al. Prevalence of retinitis pigmentosa in South Indian population aged above 40 years. Ophthalmic Epidemiol. 2008; 15:279-81.
15. Azam M, Khan MI, Gal A, Hussain A, Shah ST, Khan MS, et al. A homozygous p.Glu150Lys mutation in the opsin gene of two Pakistani families with autosomal recessive retinitis pigmentosa. Mol Vis. 2009;15:2526-34.
16. Azam M, Collin RW, Malik A, Khan MI, Shah ST, Shah AA, et al. Identification of novel mutations in Pakistani families with autosomal recessive retinitis pigmentosa. Arch Ophthalmol. 2011;129:1377-8.
17. Sharon D, Banin E. Nonsyndromic retinitis pigmentosa is highly prevalent in the Jerusalem region with a high frequency of founder mutations. Mol Vis. 2015;21:783-92.
18. Abu-Safieh L, Alrashed M, Anazi S, Alkuraya H, Khan AO, Al-Owain M, et al. Autozygome-guided exome sequencing in retinal dystrophy patients reveals pathogenetic mutations and novel candidate disease genes. Genome Res. 2013;23:236-47.
19. Belle EMS, Shah S, Parfitt T, Thomas MG. Y chromosomes of self-identified Syeds from the Indian subcontinent show evidence of elevated Arab ancestry but not of a recent common patrilineal origin. Archaeological Anthropological Sci. 2010;2:217-24.
20. Khan MI, Ajmal M, Micheal S, Azam M, Hussain A, Shahzad A, et al. Homozygosity mapping identifies genetic defects in four consanguineous families with retinal dystrophy from Pakistan. Clin Genet. 2013;84:290-3.
21. Davidson AE, Millar ID, Urquhart JE, Burgess-Mullan R, Shweikh Y, Parry N, et al. Missense mutations in a retinal pigment epithelium protein, bestrophin-1, cause retinitis pigmentosa. Am J Hum Genet. 2009;85:581-92.
22. Noor A, Windpassinger C, Patel M, Stachowiak B, Mikhailov A, Azam M, et al. CC2D2A, encoding a coiled-coil and C2 domain protein, causes autosomal-recessive mental retardation with retinitis pigmentosa. Am J Hum Genet. 2008;82:1011-8.
23. Ali M, Ramprasad VL, Soumittra N, Mohamed MD, Jafri H, Rashid Y,

et al. A missense mutation in the nuclear localization signal sequence of CERKL (p.R106S) causes autosomal recessive retinal degeneration. Mol Vis. 2008;14:1960-4.
24. Khan MI, Kersten FF, Azam M, Collin RW, Hussain A, Shah ST, et al. CLRN1 mutations cause nonsyndromic retinitis pigmentosa. Ophthalmo. 2011;118:1444-8.
25. Zhang Q, Zulfiqar F, Riazuddin SA, Xiao X, Ahmad Z, Riazuddin S, et al. Autosomal recessive retinitis pigmentosa in a Pakistani family mapped to CNGA1 with identification of a novel mutation. Mol Vis. 2004;10:884-9.
26. Khan MI, Azam M, Ajmal M, Collin RWJ, den Hollander AI, Cremers FPM, et al. The Molecular Basis of Retinal Dystrophies in Pakistan. Genes (Basel). 2014; 5:176-95.
27. Khaliq S, Abid A, Hameed A, Anwar K, Mohyuddin A, Azmat Z, et al. Mutation screening of Pakistani families with congenital eye disorders. Exp Eye Res. 2003; 76:343-8.
28. Lotery AJ, Malik A, Shami SA, Sindhi M, Chohan B, Maqbool C, et al. CRB1 mutations may result in retinitis pigmentosa without para-arteriolar RPE preservation. Ophthalmic Genet. 2001; 22:163-9.
29. Ajmal M, Khan MI, Neveling K, Khan YM, Azam M, Waheed NK, et al. A missense mutation in the splicing factor gene DHX38 is associated with early-onset retinitis pigmentosa with macular coloboma. J Med Genet. 2014;51:444-8.
30. Khan MI, Collin RW, Arimadyo K, Micheal S, Azam M, Qureshi N, et al. Missense mutations at homologous positions in the fourth and fifth laminin A G-like domains of eyes shut homolog cause autosomal recessive retinitis pigmentosa. Mol Vis. 2010;16:2753-9.
31. Bandah-Rozenfeld D, Collin RW, Banin E, van den Born LI, Coene KL, Siemiatkowska AM, et al. Mutations in IMPG2, encoding interphotoreceptor matrix proteoglycan 2, cause autosomal-recessive retinitis pigmentosa. Am J Hum Genet. 2010;87:199-208.
32. van Huet RA, Collin RW, Siemiatkowska AM, Klaver CC, Hoyng CB, Simonelli F, et al. IMPG2-associated retinitis pigmentosa displays relatively early macular involvement. Invest Ophthalmol Vis Sci. 2014; 55:3939-53.
33. Shahzadi A, Riazuddin SA, Ali S, Li D, Khan SN, Husnain T, et al. Nonsense mutation in MERTK causes autosomal recessive retinitis pigmentosa in a consanguineous Pakistani family. Br J Ophthalmol. 2010;94:1094-9.
34. Riazuddin SA, Zulfiqar F, Zhang Q, Yao W, Li S, Jiao X, et al. Mutations in the gene encoding the alpha-subunit of rod phosphodiesterase in consanguineous Pakistani families. Mol Vis. 2006;12:1283-91.
35. Ali S, Riazuddin SA, Shahzadi A, Nasir IA, Khan SN, Husnain T, et al. Mutations in the beta-subunit of rod phosphodiesterase identified in consanguineous Pakistani families with autosomal recessive retinitis pigmentosa. Mol Vis. 2011;17:1373-80.
36. Zhang Q, Zulfiqar F, Xiao X, Riazuddin SA, Ahmad Z, Caruso R, et al. Severe retinitis pigmentosa mapped to 4p15 and associated with a novel mutation in the PROM1 gene. Hum Genet. 2007;122:293-9.
37. Riazuddin SA, Zulfiqar F, Zhang Q, Sergeev YV, Qazi ZA, Husnain T, et al. Autosomal recessive retinitis pigmentosa is associated with mutations in RP1 in three consanguineous Pakistani families. Invest Ophthalmo Vis Sci. 2005;46:2264-70.
38. Khaliq S, Abid A, Ismail M, Hameed A, Mohyuddin A, Lall P, et al. Novel association of RP1 gene mutations with autosomal recessive retinitis pigmentosa. J Med Genet. 2005;42:436-8.
39. Mackay DS, Ocaka LA, Borman AD, Sergouniotis PI, Henderson RH, Moradi P, et al. Screening of SPATA7 in patients with Leber congenital amaurosis and severe childhood-onset retinal dystrophy reveals disease-causing mutations. Invest Ophthalmol Vis Sci. 2011; 52:3032-8.
40. Riazuddin SA, Iqbal M, Wang Y, Masuda T, Chen Y, Bowne S, et al. A splice-site mutation in a retina-specific exon of BBS8 causes nonsyndromic retinitis pigmentosa. Am J Hum Genet. 2010;86:805-12.
41. Ajmal M, Khan MI, Micheal S, Ahmed W, Shah A, Venselaar H, et al. Identification of recurrent and novel mutations in TULP1 in Pakistani families with early-onset retinitis pigmentosa. Mol Vis. 2012;18:1226-37.
42. Iqbal M, Naeem MA, Riazuddin SA, Ali S, Farooq T, Qazi ZA, et al. Association of pathogenic mutations in TULP1 with retinitis pigmentosa in consanguineous Pakistani families. Arch Ophthalmol. 2011;129:1351-7.
43. Singh HP, Jalali S, Narayanan R, Kannabiran C. Genetic analysis of Indian families with autosomal recessive retinitis pigmentosa by homozygosity screening. Invest Ophthalmol Vis Sci. 2009; 50:4065-71.
44. Zach F, Stohr H. FAM161A. a novel centrosomal-ciliary protein implicated in autosomal recessive retinitis pigmentosa. Adv Exp Med Biol. 2014;801:185-90.
45. Gu S, Kumaramanickavel G, Srikumari CR, Denton MJ, Gal A. Autosomal recessive retinitis pigmentosa locus RP28 maps between D2S1337 and D2S286 on chromosome 2p11-p15 in an Indian family. J Med Genet. 1999; 36:705-7.
46. Kumar A, Shetty J, Kumar B, Blanton SH. Confirmation of linkage and refinement of the RP28 locus for autosomal recessive retinitis pigmentosa on chromosome 2p14-p15 in an Indian family. Mol Vis. 2004;10:399-402.
47. Srilekha S, Arokiasamy T, Srikrupa NN, Umashankar V, Meenakshi S, Sen P, et al. Homozygosity mapping in Leber Congenital Amaurosis and Autosomal Recessive Retinitis Pigmentosa in south indian families. PLoS One. 2015;10:e0131679.
48. Gandra M, Anandula V, Authiappan V, Sundaramurthy S, Raman R, Bhattacharya S, et al. Retinitis pigmentosa: mutation analysis of RHO, PRPF31, RP1, and IMPDH1 genes in patients from India. Mol Vis. 2008;14:1105-13.
49. Saini S, Robinson PN, Singh JR, Vanita V. A novel 7 bp deletion in PRPF31 associated with autosomal dominant retinitis pigmentosa with incomplete penetrance in an Indian family. Exp Eye Res.2012;104:82-8.
50. Dikshit M, Agarwal R. Mutation analysis of codons 345 and 347 of rhodopsin gene in Indian retinitis pigmentosa patients. J Genet. 2001;80:111-6.
51. Kannabiran C, Singh HP, Jalali S. Mapping of locus for autosomal dominant retinitis pigmentosa on chromosome 6q23. Hum Genet. 2012;131:717-23.
52. Joseph B, Srinivasan A, Soumittra N, Vidhya A, Shetty NS, Uthra S, et al. RPE65 gene: multiplex PCR and mutation screening in patients from India with retinal degenerative diseases. J Genet. 2002;81:19-23.
53. Kannabiran C, Palavalli L, Jalali S. Mutation of SPATA7 in a family with autosomal recessive early-onset retinitis pigmentosa. J Mol Genet Med. 2012;6:301-3.
54. Zangerl B, Goldstein O, Philp AR, Lindauer SJ, Pearce-Kelling SE, Mullins RF, et al. Identical mutation in a novel retinal gene causes progressive rod-cone degeneration in dogs and retinitis pigmentosa in humans. Genomics. 2006;88:551-63.