SYSTEMATIC REVIEW

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

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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.

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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)

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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.

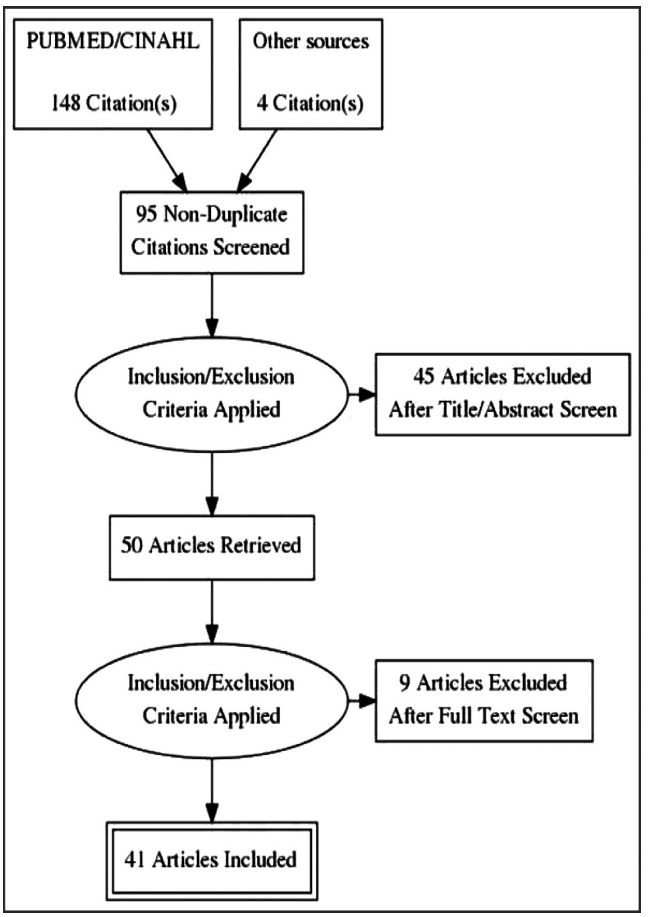

Figure: Flow chart representing literature search.

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.

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