

## Rare eye diseases in India: A concise review of genes and genetics

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Rare eye diseases (REDs) are mostly progressive and are the leading cause of irreversible blindness. The disease onset can vary from early childhood to late adulthood. A high rate of consanguinity contributes to India's predisposition to RED. Most gene variations causing REDs are monogenic and, in some cases, digenic. All three types of Mendelian inheritance have been reported in REDs. Some of the REDs are related to systemic illness with variable phenotypes in affected family members. Approximately, 50% of the children affected by REDs show associated phenotypes at the early stages of the disease. A precise clinical diagnosis becomes challenging due to high clinical and genetic heterogeneity. Technological advances, such as next-generation sequencing (NGS), have improved genetic and genomic testing for REDs, thereby aiding in determining the underlying causative gene variants. It is noteworthy that genetic testing together with genetic counseling facilitates a more personalized approach in the accurate diagnosis and management of the disease. In this review, we discuss REDs identified in the Indian population and their underlying genetic etiology.

**Key words:** Genetic analysis, genetic counseling, next-generation sequencing, rare eye diseases

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Rare Eye diseases (REDs) are heterogeneous clinical conditions which affects small numbers of individuals in general population. Although it has a low prevalence rate but have a major consequence on affected individuals. Most of RED are genetic disorders associated with autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive mode of inheritance patterns. Treatment options for RED are challenging, on the other hand early diagnosis and accurate genotype/phenotype correlations might facilitate the clinical management of disease. Here, we summarise the most common forms of REDs were found in the Indian patients with genetic abnormalities.

### Aniridia (AN)

Congenital aniridia (OMIM# 106210) is a rare panocular genetic disorder that causes variable degrees of hypoplasia or complete absence of the iris, associated with other ocular features, including optic nerve hypoplasia, cataract, and glaucoma.<sup>[1]</sup> The candidate gene for aniridia is the paired box-6 (*PAX6*) gene located in chromosome 11p13 consisting of 14 exons.<sup>[2]</sup> It is often associated with autosomal dominant inheritance or with WAGR syndrome (Wilm's tumor, aniridia, genitourinary abnormalities, and mental retardation).<sup>[3]</sup> Aniridia occurs in the general population with a frequency of 1 in 50,000 to 100,000.<sup>[1]</sup> The human *PAX6* gene is expressed in the early stages of neuroectoderm

that further differentiate into ocular tissues such as the cornea, ciliary body, lens, and retina during embryonic development.<sup>[4]</sup> In a typical aniridia phenotype, heterozygous mutations resulting in protein truncations were found in the *PAX6* gene. However, in non-aniridic phenotypes such as optic nerve hypoplasia, ocular coloboma and foveal hypoplasia missense mutations in *PAX6* are mainly observed.<sup>[5]</sup> Congenital aniridia with *PAX6* mutations is related to iris anomalies (100%), nystagmus (100%), foveal hypoplasia (94.7%), cataracts (68.4%), keratopathy (52.6%), and glaucoma (47.4%).<sup>[6]</sup> An overall *PAX6* mutation detection rate of 43.3% was reported in Indian aniridic patients with variable phenotypes.<sup>[6,7]</sup> Therefore, genetic screening of Indian families with aniridia can help in early detection and management. Presently, there is no cure for aniridia. However, treatments are available for aniridia-associated conditions, such as glaucoma, cataracts, or keratopathy.

### Corneal Dystrophies (CD)

Corneal dystrophies are inherited rare disorders of the cornea. They progress gradually, and the severity of symptoms can vary from mild to significant vision impairment. These genetic disorders are mostly inherited in an autosomal dominant manner. The primary clinical characteristic associated with corneal dystrophies is unusual deposits found in different layers of the cornea (epithelium, epithelial basement

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membrane, Bowman layer, endothelium, and Descemet membrane).

### Macular Corneal Dystrophy (MCD)

Autosomal recessive macular corneal dystrophy (MCD, OMIM# 217800) is caused by mutations in the *CHST6* gene. Biochemical studies have shown that defects in keratin sulfate as a result of mutations in coding regions of *CHST6* are predominately associated with MCD type I. Deletions and rearrangement in upstream sequences of *CHST6* are usually related to MCD type II.<sup>[8,9]</sup> Decreased visual acuity in MCD patients is due to an irregular corneal stroma and formation of focal haze leading to gray-white opacities that can be observed upon a slit-lamp examination.<sup>[10]</sup> Six novel, eight reported, and two hotspot *CHST6* mutations were identified in an Indian cohort. The study suggests high allelic and locus heterogeneity in patients with MCD.<sup>[11]</sup> Some genetic studies failed to identify the mutations in MCD patients, as a consequence of genetic heterogeneity or nucleotide variations in regulatory regions of *CHST6*.<sup>[8,12,13]</sup> Clinical treatment includes phototherapeutic keratectomy (PTK) for early stages and deep anterior lamellar keratoplasty in advanced stages.<sup>[10]</sup> Interestingly, *CHST6* homozygous missense mutation (S53L) was commonly identified in MCD families from Southern India as well as in the American population, suggesting it to be a hotspot variation.<sup>[8,11,14]</sup>

### Lattice Corneal Dystrophy (LCD) and Granular Corneal Dystrophy (GCD)

Both dystrophies are caused by mutations in the *TGFBI* gene (*TGFBI* or *BIGH3*, transforming growth factor- $\beta$  I) with autosomal inheritance. *TGFBI* is an extracellular matrix protein expressed in many tissues including the cornea. LCD (OMIM# 122200) is characterized by the accumulation of amyloid in the cornea, resulting in opacities within the corneal stroma. The opacities start at the center of the cornea and progress to the periphery. This affects corneal transparency and leads to vision impairment. LCD is inherited in an autosomal dominant manner. From a genetic analysis, 14 patients with LCD were found to have *TGFBI* sequence variations among which three are novel mutations.<sup>[15]</sup> In addition, a predominant mutation Arg124Cys was identified in Indian LCD patients and other populations.<sup>[15,16]</sup> GCD is characterized by small, circular, superficial, breadcrumb-like deposits in the stroma that develop and increase with age. Most GCD type I (OMIM# 121900) patients were identified with the Arg555Trp variant of the *TGFBI* gene with typical signs of granular opacities in the corneal stroma.<sup>[15]</sup> Additionally, a severe granular corneal dystrophy phenotype was found in patients with a family history of consanguinity and with the same *TGFBI* gene mutation (Arg555Trp).<sup>[17]</sup> GCD type II also known as Avellino corneal dystrophy (OMIM #121900) and is characterized by the presence of distinct granular deposits in the sub-epithelial and anterior stromal corneal layers with or without apparent lattice lines in the stroma.<sup>[18]</sup> R124H mutation in the *TGFBI* gene was found in two unrelated Indian families with Avellino corneal dystrophy.<sup>[19]</sup> This identified mutation was also reported in other populations such as Germany, Ireland, Europe, Japan, France, South Korea, the United Kingdom, and Iran. A *TGFBI* Arg124Leu variant was found in a patient clinically diagnosed with GCD type III (also known as Reis-Bücklers

dystrophy).<sup>[15]</sup> A clinical sign associated with multiple opacities in a honeycomb pattern was observed in sub-epithelial and superficial stromal layers.<sup>[3]</sup>

### Anophthalmia/Microphthalmia (A/M)

Anophthalmia and microphthalmia (OMIM# 251600) are congenital ocular anomalies that are responsible for childhood blindness, with an estimated prevalence of 1 per 7000 and 1 per 30,000, respectively.<sup>[20]</sup> It exhibits unilaterally or bilaterally with variable penetrance and high heterogeneity. Anophthalmia is considered when there is non-appearance of ocular tissues. The presence of a small eye within the orbit is called microphthalmia. Clinical signs are diverse and associated with a variety of developmental eye disorders, including coloboma, microcornea, sclero-cornea, cataracts, aphakia, glaucoma, aniridia, iris hypoplasia, corneal and retinal dystrophies, and optic nerve hypoplasia. Mutations in 15 developmental genes (*BMP4*, *CRYBA4*, *FOXE3*, *GDF6*, *GJA3*, *GJA8*, *MITE*, *OTX2*, *PAX6*, *PITX3*, *RAX*, *SIX3*, *SIX6*, *SOX2*, and *VSX2*) were evaluated in 52 individuals with anophthalmia and microphthalmia. Among these, the *SOX2* (Pro181Gln) mutation was found in a patient with bilateral microphthalmia. Eight novel and 14 known variations were identified from this study.<sup>[21]</sup>

### Isolated Ectopia Lentis (IEL)

Isolated ectopia lentis (IEL, OMIM# 129600) is involved in childhood visual impairment associated with irregular positioning of the lens. Affected individuals showed symptoms of irregular curvature of lens, myopia, cataract, and glaucoma. Some IEL patients exhibit retinal detachments that might lead to blindness. It has also been shown to have a connection with genetic syndromes such as Marfan syndrome and Weill-Marchesani syndrome. Autosomal-dominant IEL is mainly associated with mutations in the *FBN1* and *ADAMTSL4* genes. The protein fibrillin-1 is a structural component of microfibrils of the extracellular matrix, which is required for structural and regulatory properties of load-bearing connective tissues in humans. It is a major connector of the peripheral and equatorial areas of the lens capsule. The *FBN1* mutation (R240C) was identified in an Indian family diagnosed with IEL by using linkage mapping and gene sequencing.<sup>[22]</sup>

### Blepharophimosis Ptosis Epicanthus Inversus Syndrome (BPES)

Blepharophimosis ptosis epicanthus inversus syndrome (BPES, OMIM# 110100) is a distinct rare genetic disorder associated with eyelid dysplasia, small palpebral fissures (blepharophimosis), droopy eyelids (ptosis), and an upward folding of the lower eyelid skin close to the eye's inner corner (epicanthus inversus). It has a prevalence of about 1 in 50,000 live births with two types of occurrence. In type I BPES, the eyelid abnormalities coexist with ovarian failure, whereas type II BPES involves eyelid defects alone. While the most common inheritance pattern of BPES is autosomal dominant (AD), few sporadic cases have also been recorded.<sup>[23-25]</sup> Interestingly, the first report of recessive inheritance in BPES was documented in a South Indian family.<sup>[26]</sup> *FOXL2* gene is a putative winged helix/fork-head transcription factor gene located on chromosome 3q23. Mutations in *FOXL2* have shown allelic heterogeneity in BPES.

These were found to be associated with several intragenic variations and deletions accounting for 70% of the patients.<sup>[27]</sup> Novel homozygous *FOXL2* mutation (FOXL2–Ala19) was identified in an Indian family with type I BPES phenotype.<sup>[26]</sup>

### Primary Congenital Glaucoma (PCG)

Primary congenital glaucoma (PCG, OMIM# 231300) is a childhood blindness disorder associated with genetically determined abnormalities in the anterior chamber angle and trabecular meshwork tissue of the eye. It causes obstruction in the outflow of aqueous humor, which leads to increased intraocular pressure (IOP) and optic nerve damage with progressive vision loss. It is mostly inherited in an autosomal recessive fashion; some sporadic patients have also been reported. A higher incidence was noted in populations with a higher percentage of consanguinity. In the state of Andhra Pradesh, 1 in 3300 is diagnosed with PCG.<sup>[28]</sup> Mutations in the *CYP1B1* gene, which encodes a member of the cytochrome P450 superfamily of enzymes, were identified in PCG patients.<sup>[29]</sup> It is a major enzyme that is required to metabolize signaling molecules involved in the eye development. Mutations in the *LTBP2* gene were found in PCG patients from various populations. Screening of 54 unrelated patients with PCG from Northern India for the *LTBP2* gene did not reveal any pathogenic variants, suggesting the need for screening of additional candidate genes such as *MYOC* and *FOXC1*.<sup>[30]</sup> Five PCG patients were reported to carry a *MYOC* gene mutation (Gln48His), which shows its involvement in a subtype of glaucoma from Indian patients.<sup>[31]</sup> Digenic mode of inheritance was also identified in a PCG patient with double heterozygous variations in *CYP1B1* (Arg368His) and *MYOC* (Gln48His)<sup>[32]</sup> genes. This highlights genetic heterogeneity or association of multiple genes in Indian PCG patients. *FOXC1* is a member of the winged-helix/fork-head family of transcription factors involved in the development of the anterior segment of the eye. Interestingly, five novel mutations in the *FOXC1* gene were identified in a large cohort of PCG patients, suggesting that it might have a role in PCG pathogenesis.<sup>[33]</sup>

### Inherited Retinal Dystrophies (IRD)

Inherited retinal dystrophies (IRDs) are a group of clinically and genetically heterogeneous progressive disorders of the retina. IRDs are inherited in autosomal dominant, recessive, and X-linked manners. Retinitis pigmentosa is the most common IRD. Photoreceptor cell death is the cause of loss of vision. The disease onset ranges from congenital to late adulthood.

### Familial Exudative Vitreoretinopathy (FEVR)

Familial exudative vitreoretinopathy (FEVR, OMIM# 133780) is a well-known IRD characterized by incomplete development of the retinal vasculature. Other clinical features include retinal exudates, macular ectopia, neovascularization, fibro-vascular mass, and falciform folds. The most common inheritance of FEVR is AD.<sup>[34]</sup> FEVR is genetically heterogeneous and is caused by various gene mutations such as *NDP* (Norrie disease protein), *LRP5* (low-density lipoprotein receptor-related protein 5), *FZD4* (frizzled class receptor 4), *TSPAN12* (tetraspanin 12), and *ZNF408* (zinc finger protein 408).<sup>[35–37]</sup> Whole-exome

sequencing performed in Indian families identified four novel mutations in the *LRP5* gene.<sup>[38]</sup> Mutation screening of 110 clinically diagnosed and unrelated patients with FEVR revealed five novel and three reported variations in the coding region of the *NDP* gene.<sup>[39]</sup> A homozygous mutation (c.67-1g > c, p.L23GfsX66) leading to premature termination of the protein was found in the splice acceptor region of the *TSPAN12* gene in an Indian female patient with FEVR.<sup>[40]</sup>

### Juvenile X-linked Retinoschisis (JXLR)

Juvenile X-linked retinoschisis (JXLR, OMIM #312700) is an X-linked (OMIM# 312700) recessive disorder that occurs exclusively in males. Its prevalence ranges from 1:5000 to 1:25000. It is associated with early vision loss due to progressive macular degeneration. It is also characterized by splitting of retinal layers and reduced b-wave pattern in electroretinogram (ERG). The *RS1* gene encodes a protein called retinoschisin. The mutations in the *RS1* gene result either in misfolding of the protein or non-functional protein. Five *RS1* gene mutations were identified in JXLR patients with typical signs of retinoschisis in the peripheral and foveal region.<sup>[41]</sup> Interestingly, genetic screening of JXLR patients with developmental delay and sensorineural hearing loss revealed a pathogenic splice site mutation (c.78 + 1G > T) in the *RS1* gene.<sup>[42]</sup> This suggests that various systemic defects also coexist with the JXLR phenotype. In addition, *RS1* and *NDP* digenic inheritance have been reported in families with retinoschisis.<sup>[43]</sup> A novel *RS1* gene mutation (c. 375\_377 del AGA) was identified in a rare clinical phenotype of X-linked retinoschisis in an angle-closure glaucoma patient of Indian origin.<sup>[44]</sup> Unusual clinical manifestations of JXLR can be characterized by a combination of ERG, OCT, and family screening. Genetic analysis can help understand the genotype–phenotype correlation.<sup>[45]</sup>

### Stargardt Disease (STGD)

Stargardt disease (STGD, OMIM # 248200) causes early childhood blindness due to bilateral macular dystrophy, leading to progressive loss of central vision. The estimated prevalence of STGD is 1 in 8000–10,000. Clinical features include mottling or atrophy of the retinal pigment epithelium (RPE), fundus flavimaculatus, flecks and shiny appearance in the macula, and cone–rod dysfunction. Another important finding is the accumulation of lipofuscin content in RPE cells as a result of failure in the removal of toxic substances that eventually cause photoreceptor cell death. There are six candidate genes (*ABCA4*, *CNGB3*, *ELOVL4*, *PROM1*, *PRPH2*, and *CRB1*) associated with various types of pan-retinal dystrophies related to the STGD1 phenotype. Mutations in the *ABCA4* gene are responsible for the recessive form of STGD type I. It is a large gene, and a member of the subfamily A of the ATP-binding cassette (ABC) transporters, which is expressed in cone and rod photoreceptor cells. Genetic mutations in *ELOVL4* (elongation of very-long-chain fatty acids 4) *PROM1* (prominin 1) genes were linked to phenotypes of STGD3 and STGD4, respectively.<sup>[46]</sup> The first genetic study on Stargardt disease was carried out in India by using next-generation sequencing. In this study, five unrelated Stargardt patients and their family members were screened. Four compound heterozygous mutations and one homozygous mutation in the *ABCA4* gene were identified.<sup>[47]</sup> Another genetic study of 28 patients diagnosed with Stargardt-like phenotype revealed 75% disease-causing

mutations and 7% benign variations in the *ABCA4* gene. The remaining 18% of patients did not carry any *ABCA4* mutations, thus pointing toward the genetic heterogeneity.<sup>[48]</sup> The genetic variants identified from Indian Stargardt patients and their clinical phenotypes (genotype–phenotype correlations) were consistent with other populations.<sup>[47]</sup>

### Achromatopsia (ACHM)

Achromatopsia (ACHM, OMIM# 216900) is a rare IRD and highly heterogeneous, with a prevalence of 1 in 30,000 to 1 in 50,000. Clinical features are reduced visual acuity, photophobia, night blindness, decreased color perception, peripheral loss of vision, and central scotoma. This is caused by degeneration or loss of photoreceptors. Mutations in genes involved in the visual transduction cascade *CNGA3*, *CNGB3*, *GNAT2*, *PDE6C*, *PDE6H*, and *ATF6* of the ER stress pathway are responsible for the ACHM phenotype (<https://www.omim.org/entry/216900>). The most frequently identified gene implicated in ACHM is *CNGB3*, which has a functional role in encoding the beta subunit of the cyclic nucleotide-gated ion channel in cone photoreceptors. A spectrum of *CNGB3* mutations and copy number variations were identified in clinically diagnosed ACHM patients in different ethnic groups.<sup>[49]</sup> Using next-generation sequencing, a recurrent mutation c. 1148delC (p.Thr383fs) in *CNGB3* was identified in an Indian family with autosomal recessive cone dystrophy.

### Bardet–Biedl Syndrome (BBS)

The Bardet–Biedl syndrome (BBS, OMIM# 209900) is inherited in an autosomal recessive manner and is clinically and genetically heterogeneous. Major clinical features associated with BBS are retinal dystrophy (cone–rod type), truncal obesity, polydactyly in upper and lower limbs, intellectual impairment, hypogonadism, and renal dysfunction. In North America and Europe, BBS has a prevalence of 1 in 140,000 to 1 in 160,000 live births. However, the incidence increases in consanguineous populations.<sup>[50]</sup> There are 20 different genes in which mutations were identified in patients with Bardet–Biedl syndrome. These genes have a critical role in maintaining the structure of cilia. Mutations in the *BBS1* and *BBS10* genes were identified in the Indian population with low prevalence compared to European descents.<sup>[51,52]</sup> The extremely rare *ARL6* (ADP Ribosylation Factor Like GTPase 6, involved in cargo trafficking to the periciliary membrane) gene mutations were found in 18% of Indian patients with BBS, suggestive of the role of *ARL6* in pathogenesis and as an important candidate for genetic test.<sup>[52]</sup> In addition to this, recurrent mutations in *ARL6* (p.I91T) and in exon 2 of the *BBS10* gene were attributed as hotspot regions in Indian patients with BBS.

### Oculocutaneous Albinism and Ocular Albinism (OCA, OA)

Oculocutaneous albinism (OCA, OMIM# 203100) is an autosomal recessive inherited disease characterized by a lack of pigmentation in the skin, hair, and iris. Lack of pigmentation in the iris is called ocular albinism (OA). It is estimated that 1 in 17,000 people worldwide is affected by albinism. The clinical complications include transillumination and hypopigmentation in the iris, congenital nystagmus, astigmatism, foveal hypoplasia, and decreased visual acuity.

Candidate genes *TYR*, *P*, *MC1R*, *TYRP1*, and *SLC45A2* for OC1-4 and *GPCR143* responsible for causing OA1 (OMIM # 300500) are involved in pigment biosynthesis. Mutations in the abovementioned genes alter the melanin biosynthetic pathway, resulting in a lack of pigmentation in cutaneous and ocular regions. Mutations in the tyrosinase (*TYR*) gene cause OCA1 (OMIM # 203100). This copper-containing enzyme expressed in melanocytes controls the pigment's production. In a study with Indian subjects, four out of 23 probands (17.39%) were identified to be homozygous for a *TYR* mutation, two of which have a history of consanguinity.<sup>[53]</sup> Genetic analysis of the *TYR* gene in OCA patients from Eastern India revealed homozygous (p.Arg278 Stop) mutations along with shared common haplotypes among the affected individuals. These suggest a possible founder effect manifesting albinistic phenotypes due to *TYR* gene mutations in Eastern Indian OCA patients.<sup>[54]</sup> Further mutation screening of *SLC45A2* (solute carrier family 45, member 2) and *P* (pink-eyed dilution gene) genes exhibits several novel and reported sequence variants in OCA patients.<sup>[53-55]</sup> Most remarkably, prenatal diagnosis was established in an Indian OCA1 family with a *TYR* gene mutation (p.R239W).<sup>[56]</sup>

### Retinitis Pigmentosa (RP)

Retinitis pigmentosa (RP, OMIM# 226800) is one of the hereditary retinal dystrophies associated with degeneration of photoreceptor cells and leads to irreversible blindness. It is a progressive disease with a high degree of clinical heterogeneity. Clinical features include decreased night/day vision, progressive loss of visual acuity, and changes in fundus examination, including retinal pigment epithelium (RPE) atrophy. It is also characterized by pigmentary deposits in the intra-retinal region with unusual electroretinographic (ERG) responses. The prevalence of RP is estimated to be anywhere from 1 in 1000 to 1 in 4000 worldwide. Prevalence of blindness due to RP was observed to be 1 in 1000 in South India.<sup>[57]</sup> More than 85 genes are known to cause non-syndromic RP with autosomal and X-linked forms of inheritance (<https://omim.org/entry/268000>). The highest degree of genetic heterogeneity was observed in Indian patients with autosomal recessive RP (arRP) compared to other forms.<sup>[58]</sup> Mutations in *TULP1*, *NR2E3*, *MFRP*, *ABCA4*, and *RP1* genes were identified in Indian patients with arRP by genome-wide homozygosity mapping.<sup>[58,59]</sup> Whole-exome sequencing (WES) identified several mutations in the *EYS* and *FAM161A* genes in sporadic and arRP patients.<sup>[60,61]</sup> Interestingly, early-onset of arRP was observed in patients with *SPATA7* gene (spermatogenesis-associated protein 7) mutations.<sup>[62]</sup> A novel (p.Cys299Tyr) *PRPF31* gene mutation was identified in autosomal dominant RP (adRP) with incomplete penetrance in a North Indian family.<sup>[63]</sup> Genetic analysis of a patient with severe childhood-onset RP with a consanguineous family history revealed an autosomal recessive mutation (p.Tyr549Ter) in the *MERTK* gene.<sup>[64]</sup> Homozygosity mapping-guided next-generation sequencing identified a novel mutation in the *CDHR1* (cadherin-related family member 1) gene associated with arRP.<sup>[65]</sup>

### Leber's Congenital Amaurosis (LCA)

Leber's congenital amaurosis (LCA, OMIM #204000) is the most common IRD in children. A higher incidence rate was observed in South India owing to its consanguineous marriage

practice.<sup>[66]</sup> The estimated prevalence of LCA was 2–3 per 100,000 live births. Clinical features of LCA are nystagmus, absence of pupillary responses, reduced visual acuity, high hyperopia, photophobia, and non-recordable ERG. It is a severe form of retinal dystrophy causing blindness at the age of 1 year. LCA is highly heterogeneous clinically and genetically with phenotypes similar to other early-onset childhood retinal dystrophies. Twenty-nine candidate genes (*AIPL1*, *ALMS1*, *CABP4*, *CCT2*, *CEP290*, *CNGA3*, *CLUAP1*, *CRB1*, *CRX*, *DTHD1*, *GDF6*, *GUCY2D*, *IQCB1*, *IMPDH1*, *IFT140*, *KCNJ13*, *LCA5*, *LRAT*, *MERTK*, *MYO7A*, *NMNAT1*, *OTX2*, *PRPH2*, *RD3*, *RDH12*, *RPE65*, *RPGRIP1*, *SPATA7*, and *TULP1*) were reported in LCA patients with autosomal recessive inheritance. Mutations in *CRX*, *IMPDH1*, and *OTX2* genes were associated with AD inheritance patterns. LCA genetic studies have identified mutations in several candidate genes in the Indian population.<sup>[67-71]</sup> Genetic mutations identified in LCA patients from Northern America are extremely rare (2.6%) in Indian patients with LCA.<sup>[72]</sup> Interestingly, digenic inheritance (*AIPL1*, *KCNJ13*) was also found in an LCA family by using high-throughput targeted resequencing.<sup>[73]</sup> Due to their overlapping phenotypes with other retinal dystrophies, genetic screening and genetic counseling of LCA patients can help with accurate diagnosis, clinical management, carrier testing, and prenatal diagnosis.

## Therapeutic Advances in Rare Eye Diseases

Recent studies from ocular stem cell research suggest that inducible pluripotent stem cells (iPSC) might be a promising therapeutic approach for RADs in India. Successful development of corneal and retinal organoids would aid in understanding the pathological process of disease and alternative therapeutic options. A recent study from India reported that mini-corneal organoids were developed efficiently from iPSC in a three-dimensional, suspension medium.<sup>[74]</sup> The discovery of mini-corneal organoids might help in treating RADs related to the cornea. Another study describes an effective method of development of iPSC-derived retinal pigment epithelial (RPE) cells for the treatment of retinal disease.<sup>[75]</sup> In addition to that iPSCs were developed from peripheral blood mononuclear cells (PBMC) of patients with inherited retinal dystrophies.<sup>[76]</sup> These reports reveal emerging evidence of stem cell therapy in India. In 2017, the US Food and Drug Administration (FDA) approved Luxturna, a gene therapy product for *RPE65*-associated LCA (<https://clinicaltrials.gov/ct2/show/NCT00999609>). In 2019, the Indian Council of Medical Research (ICMR) launched the “National Guidelines for Gene Therapy Product (GTP) Development and Clinical Trials.” This might open new avenues for gene therapy research in India. Recently, adeno-associated virus (AAV) vector-mediated gene therapy was established *in vivo* for the selective myofibroblast apoptosis to reduce corneal haze.<sup>[77]</sup> Gene editing by CRISPR/Cas9 system has been widely explored in non-ophthalmic diseases in India. Hence, it is possible that scientists might utilize gene-editing techniques in the near future. Interestingly, gene editing might be a useful therapeutic tool for autosomal dominant, recessive, and X-linked ophthalmic diseases.

## Conclusion

Occurrence of phenotype to genotype variability can be high in India owing to its consanguinity practices, thereby increasing

the disease burden when compared to Western populations. While technologies such as NGS have facilitated a quantum leap in RED diagnostics, the intricacies of phenotype-genotype interplay are not conclusively solved. Genetic databases and prediction tools have helped with arriving at possible, yet at times, inconclusive diagnoses. In a situation like this, it becomes essential to establish a demographically relevant genetic variant database that can further substantiate a diagnosis. This review summarizes the progress in the identification of variants and their correlation to the phenotype in Indian subpopulations. From the patient service standpoint, there is a need for appropriate genetic testing and genetic counseling to help patients comprehend the disorder in question, clinically as well as genetically. Thereby, empowering them to make informed medical and personal choices.

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## Conflicts of interest

There are no conflicts of interest.

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