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REVIEW ARTICLE

Ophthalmic Genetics in Transition: Clinical Impact, Challenges and Future Outlook

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ABSTRACT

Over the past three decades, advances in diagnostic technologies have significantly improved the identification of genetic ocular disorders, strengthening the convergence of ophthalmology and clinical genetics. As ophthalmic genetics emerges as a distinct subspecialty, highlighting the rising need for clinicians with expertise in this area, this review summarizes its core principles and the evolution of diagnostic approaches, including next-generation sequencing. Through selected case examples we illustrate how molecular findings refine clinical diagnoses. Additionally, this review also addresses key challenges in ocular genetics and the solutions being implemented to address them. Together, this review highlights the importance of multidisciplinary collaboration in improving care for individuals with genetic ocular disorders.

KEYWORDS

• Ophthalomology • Genetics • Next generation sequencing

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INTRODUCTION

Genetics has played a pivotal role in understanding human ophthalmological disorders and their management, including the advent of gene therapy. The earliest documented descriptions of inherited eye diseases—such as colour blindness (1798)[1], retinitis pigmentosa (1853–1857)[2,3], Usher syndrome (1858)[4,5], and hereditary cataracts (1913)[6]—appeared during the 19th century, when ophthalmologists began correlating clinical findings with family pedigrees, long before molecular evidence was available.

The molecular era of ophthalmic genetics began in the late 20th century, with the identification of mutations in the *RHO* and *CHM* genes in 1990.[7,8] This was followed by discoveries in congenital cataracts and other inherited retinal dystrophies (IRDs), facilitated by linkage analysis and, later, next-generation sequencing in the 1990s.[9] A major milestone was the publication of the first comprehensive clinical genetic synthesis for ocular syndromes in *GeneReviews* in 1999, beginning with Usher syndrome[10]. This period marked a turning point—from purely clinical case descriptions to molecularly confirmed diagnoses—enabling precise genotype–phenotype correlations and laying the foundation for gene-based therapies.

Depending on the underlying defect—whether chromosomal, single-gene, mitochondrial, repeat expansion, epigenetic, or multifactorial—genetic eye disorders are characterized by distinct molecular mechanisms and clinical manifestations. A deep understanding of ophthalmic genetics is essential to elucidate their pathogenesis, inheritance, and prognosis, thereby guiding clinical, supportive, and rehabilitative management and reducing uncertainty and emotional stress for affected families.[11]

From common ocular diseases to complex syndromes, many conditions have a strong hereditary basis and significant genetic heterogeneity. Advances in ocular genomics have now made molecular diagnosis, as well as prenatal and preimplantation genetic testing, increasingly feasible. In parallel, insights into eye development and novel therapeutic technologies and clinical trials have also opened new therapeutic avenues including gene therapy, stem cell-based therapy, and targeted pharmacological approaches for transforming patient personalized care. Despite these achievements, much remains to be discovered about the genes and pathways governing eye development and function, underscoring the close alliance between ophthalmologists and clinical geneticists to provide comprehensive support to the affected families. In this review, we summarize key principles of ophthalmic genetics and recent diagnostic advances, illustrating through selected case examples how molecular insights can profoundly reshape clinical practice.

Basic Concepts of Genetics and their Application in Clinical Ophthalmology[12]

With genetics advancing at a remarkable pace, ophthalmologists must remain familiar with its principles and clinical applications. Globally, an estimated 30–50% of paediatric blindness and a significant proportion of adult visual impairment are caused by genetic factors[13-17]. Strengthening genetic literacy among ophthalmologists will improve diagnostic precision, facilitate timely referrals, and the delivery of compassionate, individualized patient care.

Understanding genetics begins with knowing the structure and function of chromosomes and genes. Chromosomes are composed of double-stranded DNA, which carries the genetic code through a sequence of four nucleotides—adenine (A), guanine (G), thymine (T), and cytosine (C). In RNA, uracil (U) replaces thymine. Small functional segments of DNA, known as genes, occupy specific locations on chromosomes. Each gene is transcribed into messenger RNA (mRNA), which is then translated into proteins that perform vital structural and functional roles in the body.

A gene typically consists of a promoter region that regulates its activity, exons that encode proteins, and introns, which are non-coding sequences. Genetic abnormalities or mutations can alter these normal processes and lead to disease. Mutations may involve large or small chromosomal deletions, duplications, or point mutations such as missense, nonsense, or frameshift changes. Occasionally, mutations in intronic regions disrupt normal splicing, leading to abnormal gene expression and, ultimately, clinical disease.

Mutations can be inherited from one or both parents or occur spontaneously (de novo) as new events. A mutation is termed novel when it has not been previously reported in the scientific literature. Family pedigrees, often charted over three generations, are invaluable in identifying the mode of inheritance and assessing recurrence risk.

Chromosomal disorders are usually de novo, often resulting from somatic or germline mosaicism. Somatic mosaicism, in which genetic changes occur after conception, is rarely transmitted across generations. However, chromosomal abnormalities can be inherited if a parent carries a balanced chromosomal rearrangement or, less commonly, through germline mosaicism.

Inherited ophthalmic conditions may follow several recognizable patterns of transmission, each with distinct implications for families.

- Autosomal dominant disorders occur when a single copy of an altered gene is sufficient to cause disease. These mutations are not always inherited; if they arise after conception and are not present in gametes, they are termed *de novo* mutations. Interestingly, some autosomal dominant conditions manifest only when a "second hit" occurs in the other allele—such as in retinoblastoma, where loss of heterozygosity leads to tumor development.
- Autosomal recessive disorders manifest only when both copies of the gene are affected, one from each parent, who are usually unaffected carriers. Classic examples include Leber congenital amaurosis, Stargardt disease, and Usher syndrome, all of which can cause early and severe vision loss.
- X-linked recessive disorders primarily affect males, who have only one X chromosome. Female carriers usually do not show symptoms but may be mildly affected due to skewed X-inactivation or in cases of Turner syndrome. Ocular albinism exemplifies this pattern.
- X-linked dominant disorders typically cause disease in heterozygous females, while affected males often have a more severe phenotype or may not survive.
- Mitochondrial inheritance affects both males and females, but transmission occurs exclusively through the mother. Examples include Kearns–Sayre syndrome and Leber hereditary optic neuropathy (LHON).

More complex inheritance patterns are also recognized.

- **Digenic inheritance** involves mutations in two different genes, as seen in some forms of retinitis pigmentosa.
- **Triallelic inheritance**, such as in Bardet–Biedl syndrome, involves mutations in two alleles of one gene plus one mutation in a second gene.
- **Polygenic inheritance** results from the cumulative effect of mutations in multiple genes.
- **Triplet repeat disorders**, such as myotonic dystrophy, exhibit genetic anticipation—where an increase in repeat sequences over generations leads to earlier onset and more severe disease.

Epigenetic eye disorders arise not from changes in DNA sequence but from alterations in gene expression—through mechanisms like DNA methylation, histone modification, or non-coding RNAs. These changes can activate or silence genes, influencing ocular development and disease progression. Environmental factors such as oxidative stress, maternal nutrition, or intrauterine exposure can modify these epigenetic patterns. For instance, congenital glaucoma and certain forms of retinal degeneration have been associated with epigenetic dysregulation. This emerging field provides hope that some epigenetic changes may eventually be reversible, offering new therapeutic opportunities.

Multifactorial eye disorders result from a complex interplay between genetic predisposition and environmental influences. Unlike Mendelian disorders, they do not follow a single pattern of inheritance. Common examples include age-related macular degeneration (AMD), primary open-angle glaucoma, diabetic retinopathy, and myopia. These conditions reflect the combined effects

of genetics, aging, lifestyle, and environmental exposures, underscoring the need for a holistic, patient-centred approach.

Gene-Disease Associations & Evidence Mapping

Establishing a valid gene–disease association is a critical prerequisite for interpreting individual sequence variants, as it provides the biological and clinical context needed to assess whether a genetic alteration can plausibly explain a patient's phenotype. Robust gene–disease relationships are built on strong human genetic evidence, including recurrent identification of pathogenic variants in unrelated affected individuals, segregation of variants with disease within families, and consistent clinical presentation across cohorts. These data are further supported by experimental evidence demonstrating gene expression in relevant ocular tissues, biological functions aligned with the observed phenotype, and functional or animal models that recapitulate key disease features. Together, such evidence allows gene–disease relationships to be classified as well established, moderately supported, or still evolving.[18-20]

In ophthalmology, many disease-causing genes show strong biological plausibility and reproducible genotype–phenotype correlations across populations. For example, **CNGA3** is a well-established cause of autosomal recessive achromatopsia, supported by extensive human genetic data, functional studies demonstrating impaired cyclic nucleotide-gated channel activity, and animal models closely resembling the human phenotype.[21] Similarly, **VSX2,** a transcription factor critical for early eye development, has been repeatedly implicated in autosomal recessive microphthalmia, with concordant findings from human studies and experimental models.[22]

Genes affecting structural integrity of ocular tissues further illustrate robust gene–disease relationships. **ADAMTSL4**, which contributes to zonular fibre stability, has been consistently associated with autosomal recessive ectopia lentis and ectopia lentis et pupillae, supported by recurrent loss-of-function variants and a highly specific ocular phenotype.[23] In syndromic ocular surface disease, **LAMA3** is a definitive disease gene for junctional epidermolysis bullosa with laryngo-onycho-cutaneous involvement, including characteristic ocular manifestations, supported by both human genetic evidence and experimental data.[24]

In contrast, some retinal dystrophy genes highlight the complexity of genotype–phenotype correlations. **CERKL**, associated with autosomal recessive retinitis pigmentosa, demonstrates considerable phenotypic variability despite convincing genetic evidence, likely reflecting incomplete understanding of disease mechanisms and modifying influences.[25] Similarly, **AIPL1** is a well-established retinal dystrophy gene, yet discordance between molecular findings and clinical presentation in individual cases underscores the importance of integrating genetic results with detailed phenotyping and inheritance patterns.[26]

Systematic evaluation of gene–disease evidence is essential in the era of next-generation sequencing, where multiple candidate variants may be identified in a single individual. Such findings may represent modifier effects, blended phenotypes, or incidental associations rather than a single causal diagnosis. Integrating gene–disease validity with detailed phenotyping, family history, and segregation analysis helps prioritise the most biologically and clinically plausible diagnosis and identify cases requiring additional investigations, such as copy number or structural variant analysis.[27]

A structured summary of representative gene–disease associations discussed in this review is provided in **Supplementary Table X**, while additional genes implicated in ocular disorders across the anterior and posterior segments are listed in **Supplementary Table Y**.

The assessment pathway of a genetic eye disorder:

Genetic eye disorders may occur either as isolated conditions or as part of a broader genetic syndrome. Evaluating a patient with a suspected genetic eye disorder can often be a complex and time-consuming process, requiring careful clinical, genetic, and sometimes multidisciplinary assessment. Figure 1 illustrates the intricate and often prolonged journey that patients and clinicians undertake to achieve a definitive genetic diagnosis in rare inherited ophthalmic diseases.

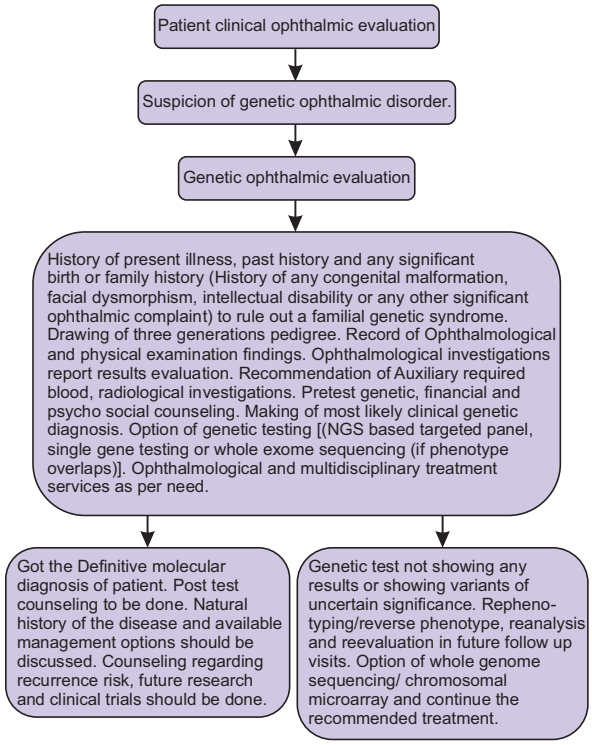


Figure 1: The assessment pathway for a genetic eye disorder, highlighting the steps from clinical evaluation to definitive molecular diagnosis

From Conventional to Advanced Genetic Testing: Applications in Clinical Ophthalmology[12]

Genetic testing has advanced rapidly from conventional cytogenetic methods to modern genomic technologies. This technological progress has deepened our insight into how the three-dimensional structure and function of chromosomes influence gene regulation, disease mechanisms, and genome evolution.

A. Conventional Cytogenetic Testing

1. **Karyotyping**

   Karyotyping is a traditional, culture-based cytogenetic technique used to visualize entire chromosomes under a microscope. It enables the detection of **numerical** (e.g., trisomies, monosomies) and **structural abnormalities** (e.g., translocations, inversions, deletions, duplications). Although fundamental to genetic diagnostics, its resolution is limited to large chromosomal changes (typically >5–10 Mb).

2. **Fluorescence In-Situ Hybridization (FISH)**

   FISH is a **probe-based hybridization technique** in which fluorescently labelled DNA probes bind to specific chromosomal regions of interest. This allows targeted detection of abnormalities that are not identifiable by karyotyping, such as **microdeletions, duplications, or specific gene rearrangements.** FISH remains valuable in confirming known chromosomal anomalies or in rapidly testing for suspected syndromes.

B. Molecular Cytogenetic Testing

1. **Multiplex Ligation-dependent Probe Amplification (MLPA)**

   MLPA is a targeted, probe-based molecular technique designed to detect specific chromosomal or gene sequence variations. After probe ligation, hybridization and amplification allow simultaneous assessment of multiple DNA regions. MLPA can detect microdeletions, insertions, duplications, methylation defects (using methylation-sensitive MLPA), mRNA expression changes, and even single nucleotide polymorphisms (SNPs). It is a rapid, efficient, and cost-effective approach for many targeted analyses.

2. **Chromosomal Microarray Analysis (CMA**

   CMA, which includes Comparative Genomic Hybridization (CGH) and SNP arrays, enables genome-wide assessment for copy number variations (CNVs). It measures the ratio of fluorescent signals between patient and control DNA, identifying unbalanced microdeletions and duplications as small as 50–100 kb. However, CMA has limitations of not detecting balanced chromosomal rearrangements, point mutations, or small insertions/deletions within single genes. Despite these constraints, it remains a first-line investigation for unexplained developmental or syndromic ocular disorders.

C. Triple-Primed Polymerase Chain Reaction (TP-PCR)

TP-PCR is a specialized molecular technique used to identify trinucleotide repeat expansion disorders, which may involve ocular manifestations. Conditions such as myotonic dystrophy, Friedreich's ataxia, and Fragile X syndrome are examples.

TP-PCR uses a locus-specific primer and a repeat-targeted primer to amplify the DNA region of interest, producing a ladder-like pattern of fluorescently labelled fragments that are separated by capillary electrophoresis. Expanded alleles produce a continuous pattern of peaks extending beyond the normal range, allowing rapid, accurate, and cost-effective detection of these repeat expansion disorders—often missed by conventional PCR.

D. Nucleotide Sequencing-Based Methods

1. Sanger Sequencing

Sanger sequencing, the classic DNA sequencing method, relies on a modified polymerase chain reaction (PCR) using chain-terminating dideoxynucleotides (ddNTPs) and capillary electrophoresis. It remains the gold standard for confirming known or suspected point mutations, small deletions, or duplications in specific genes. However, its limitations include low throughput and high cost, making it unsuitable for large-scale or genome-wide analyses.

2. Next-Generation Sequencing (NGS

NGS represents a major technological advance, allowing massively parallel, high-throughput sequencing of DNA and RNA. It can analyze thousands of genes simultaneously, providing comprehensive data on genome structure, gene expression, and genetic variation.

It provides an unbiased, powerful approach to discover novel disease genes, identify complex variants, and guide personalized treatment strategies and helps select patients for clinical trials.

NGS has revolutionized ophthalmic genetics by enabling targeted gene panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS) for inherited eye diseases (Figure 2). Targeted panels focus on selected target gene regions, while WES examines all coding regions—where nearly 80% of disease-causing variants are found. These methods offer a faster, less laborious, and far more cost-effective alternative to whole-genome sequencing (WGS), which, though powerful and capable of identifying novel genes, remains complex and expensive for routine clinical use.[28] In real-world clinical practice, targeted NGS panels and WES allow for the rapid and accurate identification of genetic variants responsible for inherited eye diseases—often within a timeframe that truly matters for patients and families seeking answers.[29]

Intron—Exon—Intron—Exon Whole Genome

Exon—Exon—Exon—Exon Whole Exome

Exon—Exon—Exon—Exon Target Exome

Figure 2: Whole Genome sequences all DNA, Whole Exome targets all coding regions, and Target Exome focuses on specific disease-related genes using Next Generation Sequencing (NGS).

The availability of these tests has brought genetics closer to everyday ophthalmic care, bridging the gap between laboratory science and patient experience. Importantly, such testing not only refines or corrects earlier clinical diagnoses but also offers clarity and reassurance to families, especially in communities where limited resources, awareness, or cultural beliefs may have long delayed an accurate diagnosis.[30,31] In our article (Case 1, Table 1), the initial clinical diagnosis was homocystinuria, but subsequent molecular testing revealed the true diagnosis to be Ectopia Lentis. This finding underscores how accurate molecular diagnosis can profoundly change medical management and, in many cases, transform patient outcomes, as supported by previous reports.[32]

The integration of Whole-Exome Sequencing (WES) with analyses for copy number variations (CNVs) and mitochondrial DNA sequencing has established WES as a first-tier diagnostic tool for many genetic disorders. Beyond diagnosis, such approaches now enable real-time, non-invasive monitoring of genetic changes in conditions such as ocular cancers also. Moreover, Next-Generation Sequencing (NGS) plays a central role in advancing personalized medicine—for instance, through gene-specific therapies like those targeting RPE65 mutations, which helps clinicians anticipate treatment response and tailor therapies accordingly for individual patients. Importantly, NGS can also identify pathogenic variants in healthy children long before disease onset, facilitating early intervention, monitoring, and awareness.[33,34]

In addition, NGS often uncovers multiple or

unexpected genetic variants, revealing complex inheritance patterns such as compound heterozygosity or the influence of modifier genes. These insights help in explaining why disease severity may vary between family members, improving our understanding of each unique patient's journey.[35,36]

The diagnostic yield of NGS differs across ocular disease categories. The highest rates are seen in hereditary retinal dystrophies up to 78%, with variability across conditions such as retinitis pigmentosa and Leber congenital amaurosis. In ocular cancers (e.g., retinoblastoma, uveal melanoma) and syndromic disorders (e.g., Usher or Hermansky-Pudlak syndromes), yields range from 52%–78%. For anterior segment disorders, the yield is around 47%, while in infantile nystagmus syndrome (INS), targeted NGS panels achieve approximately 35%.[37,38,39,40] The variability in diagnostic yield reflects several influencing factors—population diversity, phenotypic heterogeneity, age at diagnosis, family history, and technological advancements in testing.[37,35,41-46]

Nucleotide sequence variants may be pathogenic (mutations), benign (polymorphisms), or of uncertain significance. Encouragingly, reverse phenotyping, careful genotype–phenotype correlation, and periodic reanalysis can uncover novel variants, new disease genes, and previously unrecognized phenotypes, gradually improving diagnostic yields.[38,45,47] For instance, Ordoñez-Labastida *et al*. reported that the diagnostic yield of Whole-Exome Sequencing (WES) increased from 51% to 58% after reanalysis—demonstrating the value of persistence and evolving analytical tools in shortening the diagnostic journey.[38]

The accuracy of WES relies on robust standards, including high-quality DNA extraction, optimized sequencing platforms, and strong bioinformatics pipelines with reliable in silico prediction tools.[27,48] Bioinformatic re-evaluation and in silico modelling further enhance interpretation by predicting how missense or truncating variants affect protein folding and function. Supported by functional studies, these methods help reclassify variants of uncertain significance (VUS), enabling more precise and compassionate patient care.[49] Key resources, clinical databases, and AI tools relevant to genetic eye disorders are summarized in **Supplementary table Z**.

Emerging Long-Read and Optical Genomic Technologies in Ocular Genetics

Recent advances in third-generation sequencing, including long-read genome sequencing (LR-GS) and high-resolution capabilities, enable accurate detection of structural variants, complex rearrangements, and epigenetic modifications that conventional methods often miss.[50] LR-GS such as Oxford Nanopore Technologies (ONT) and Optical Genome Mapping (OGM), have expanded the scope of molecular diagnostics in ophthalmology. Together, ONT and OGM offer complementary, cost-effective tools that enhance diagnostic accuracy, illuminate disease mechanisms, and advance the promise of precision medicine in ocular genetics.

ONT allows rapid, high-resolution genomic and metagenomic analysis and real-time sequencing of large genomic regions, capturing both genetic and epigenetic information in a single run. It sequences DNA or RNA by passing strands through nanopores in a membrane, where ionic current changes are decoded in real time to reveal the nucleotide sequence. It is particularly useful for identifying complex rearrangements, compound heterozygosity, and parent-of-origin effects in disorders such as retinoblastoma.[51]

OGM, meanwhile, detects large-scale structural variants and precisely maps genomic breakpoints by generating fluorescent DNA barcodes compared against reference genomes. This technique has revealed previously undetected variants, such as USH2A gene inversions, refining genetic diagnosis in inherited retinal disorders.[53,54]

Genetic Counselling and Multidisciplinary Care:

Because many ophthalmologists may hesitate to counsel families affected by genetic eye diseases, genetic counselling becomes a crucial and comprehensive tool to educate and support them. Genetic counselling always plays a fundamental and pivot role beyond the various diagnostic techniques. It helps families understand the disorder, the available management options, and the emotional and practical aspects of living with it, enabling them to accept, adapt, and change their attitude toward the condition. Along with counselling,

multidisciplinary care involving ophthalmic imaging, electrophysiology, genetic testing, low-vision rehabilitation, supportive and specialty referral services, psychosocial and financial support, and guidance about national programs like the National Policy for Rare Diseases (NPRD), 2021, can significantly improve patient's health journey. These integrated services empower families to navigate social, emotional, and financial challenges while encouraging informed participation in research and emerging therapies. Ensuring that ethical, cultural, and legal considerations are also addressed further strengthens the delivery of holistic, patient-centred care.[29,55,56]

Table 1 Highlights representative cases that underscore the role of genomics in elucidating the molecular basis of inherited ophthalmic disorders, guiding precision treatment strategies, improving patient outcomes, and offering opportunities for prenatal diagnosis in subsequent pregnancies.

Table 1: Describing selected cases that exemplify the value of genomic approaches in establishing molecular diagnoses in ophthalmic genetics

Gender	Age	Consanguinity	Symptoms	Family History	Investigations	Genomic Diagnosis	Management
Male	8 years	Absent	Visual impairment, Superio-temporal subluxated cataractous lens, Ectopia lentis, Defect in methyl cobalamin formation or Defect in methionine synthase or in methionine synthase reductase or Methionine adenosyl transferase defect or Methylenete trahydrofolate reductase (MTHFR) deficiency leading to homocystinuriawas suspected	A sibling with cataract	Serum Homocysteine level of 28.6 µmol/L, methionine levels normal, 2D echo normal	ADAMTSL4: c.2472_2559+17del x 29 Splice Donor Homozygote/Autosomal recessive (AR) Likely Pathogenic (PVS1, PM2, PS1 and PP3) Ectopia lentis et pupillae	Sequential Lensectomy with anterior vitrectomy and correction of the aphakia with scleral fixated intraocular lens (IOL) was planned. Adequate refractive correction with bifocals was prescribed. Surveillance for assessment of visual acuity and intraocular pressure three times per year was advised. Sanger Sequencing for the affected sibling and carrier testing for parents targeted mutation was advised. Risk of 25% for similar disease in the next pregnancy explained.
Male	4 Years	Present	Microphthalmia, decreased vision since birth. Antenatal scan showed bilateral microphthalmia. Birth history is not significant. Motor and language development is delayed	Mother had 1 stillbirth at 7 months of gestation, Baby had syndactyly, absent eyeball no socket. Currently, the mother is 18 weeks pregnant, the scan shows B/L hypo ophthalmia	2D echo and ultrasound whole abdomen was normal	VSX2: c.589C>T p.Gln197Ter [40X/40X] Homozygous/ AutosomalrecessiveLikely pathogenic (PVS1, PP5, PM2) Microphthalmia, isolated 2	Management by a multidisciplinary team of specialists, including ophthalmologists, pediatricians and clinical geneticists was done. B scan of orbits was done to rule out orbital cysts. Parents were counseled that there is no definitive treatment for vision in cases of microphthalmia. Information about socket expansion using enlarging cosmetic shells/ conformers to minimize facial deformity was given to the family. Risk of 25% for similar disease in the current pregnancy was explained. Parental segregation and Amniocentesis as prenatal diagnosis for foetal molecular diagnosis was advised.

table cont....

Gender	Age	Consanguinity	Symptoms	Family History	Investigations	Genomic Diagnosis	Management
Male	24 Years	Absent	Decreased visual acuity and colour discrimination loss since early childhood. History of photophobia is present on eye examination, patient was clinically suspected to be a case of? Anisometric amblyopia, ? Achromatopsia.	Mother, two maternal uncles have similar condition.	Refractive Error: Right Eye (RE): -5.25 DS / -2.25 DC × 20° Left Eye (LE): -4.25 DS / -2.75 DC × 165° Indicates compound myopic astigmatism. Best Corrected Visual Acuity (BCVA): 6/36 in both eyes. Fundus examination: Disc and macula healthy.	CNGA3(+) c.1306C>T (p.Arg436Trp) Exon 8 Homozygous/Autosomal Recessive Pathogenic (PP1, PM3,PS3, PM2, PP3, PP2, PP5, PM5) Achromatopsia2	To reduce photophobia photochromatic glasses were prescribed. To improve visual acuity; low vision aids such as dome magnifier and telescopes;were advised.
Male	44 Years	Absent	Diminution of vision in both eyes (RE>LE) since childhood. Diificulty in seeing in dark since 20 years. Complaint of Floaters in both eyes since 20 years of age. Defective colour vision in B/E Decreased peripheral vision both eye.	The maternal grandmother's brother was affected by a similar condition.	Fundus - Pigmentary deposits resembling bone spicules in peripheral area. -Attenuation of the retinal vessels - Waxy pallor optic disc. Right eye Vision - 1/60 Left eye Vision - 2/60	CERKL c.967_968del AT: Pathogenic PM2, PVS1 & PP5 c.895G>T: Uncertain significance PM2 & PP3 Compound Heterozygous/Autosomal Recessive Retinitis pigmentosa 26	Adequate refractive error was prescribed. Low vision aids such as digital pocket magnfier and telescopes were prescribed. Yearly dilated retinal screening with daily Vitamin A supplementation of 15,000 IU was advised.
Female	38 years	Absent	Recurrent eye redness and pain (L>R) since one year of age. Difficulty in opening left eye for the last one year and right eye for the last three months. History of hoarseness of voice since childhood for which Laryngoscopy was done, malocclusion of teeth and nail dystrophy. On examination, Left pyogenic Granuloma with symblepharon (L>R)	not significant	RBS 80 mg % Eye examination: Visual acuity Right eye : 6/12. Left eye- Finger Counting at 1 meter → Right eye - no glow Left Fundus: Optic disc: Cup-to-disc ratio 0.3 (normal, not suggestive of glaucoma). Left eye Vessels: AV ratio 2:3 (normal, no significant narrowing). Left Retina: No neovascularization → no signs of proliferative diabetic retinopathy. ASOCT shows one eye with a very thin cornea (485 µm) and the other eye with a very thick cornea (809 µm, oedematous).	AIPL1 (-) : c.94C>T p.Arg32* Heterozygous Autosomal Dominant/ Autosomal Recessive Likely Pathogenic (PVS1, PM2) Cone-rod dystrophy (# 604393) LAMA3 (+) :c.133C>T p.Gln45* Heterozygous Autosomal Recessive Likely Pathogenic (PVS1, PM2) Epidermolysis bullosa, junctional 2C, laryngo-onycho-cutaneous (# 245660)	Left eye Pyogenic Granuloma excision with symblephron release with Pannus removal with Amniotic Membrane Transplantation (AMT) was done. a large-diameter bandage contact lens was inserted, and preservative-free dexamethasone 0.1% and moxifloxacin0.5% Six times in slow tapering dosestimes daily was prescribed topically. Copious lubricants were prescribed in both eyes. Topical and systemic corticosteroids have been usedfor hoarseness of voice and nail dystrophy.

table cont....

Gender	Age	Consanguinity	Symptoms	Family History	Investigations	Genomic Diagnosis	Management
			.		C-ANCA - Normal P-ANCA - Normal ANA - Positive RA factor - Normal Possibility ofLaryngo-onycho-cutaneous Syndrome (LOCS) B/E Pyogenic Granuloma with symblephron release was considered.		

Variants Potentially Modifying Phenotypes:

The above cases were interpreted against the established gene–disease relationships in ophthalmic genetics, matching clinical features with molecular findings, inheritance patterns, and family history. In some cases, incomplete genotype–phenotype concordance and the presence of multiple candidate variants highlighted the limitations of variant-level interpretation alone and also raises the possibility of modifier effects or unrecognised additional variants.

In case 5 (Table 1) analyzed by NGS/WES, two likely pathogenic heterozygous variants were detected: AIPL1:c.94C>T (p.Arg32*), associated with autosomal dominant/recessive cone-rod dystrophy, and LAMA3:c.133C>T (p.Gln45*), associated with autosomal recessive epidermolysis bullosa, junctional 2C, laryngoonychocutaneous type.

The **AIPL1** variant shows both dominant and recessive inheritance, but no segregation analysis was performed, and the patient's phenotype was inconsistent with cone-rod dystrophy. This emphasizes the importance of broad sequencing approaches rather than focusing on a single candidate gene, as modifier genes, genetic heterogeneity, and multigenic inheritance can complicate molecular diagnoses and genotype–phenotype correlations.[57,58]

Although the LAMA3 variant aligns with the clinical features, its heterozygous state cannot explain the disease, which requires homozygosity. Accurate diagnosis, therefore, demands a careful review of NGS data to rule out potential copy number variants (CNVs) such as deletions, duplications, or complex rearrangements. Even though commercial laboratories use specific CNV detection pipelines, this case highlights the need to confirm suspected CNVs. variants of uncertain significance or masked alleles using complementary techniques like qPCR, MLPA, or targeted array-CGH to resolve atypical or complex inheritance patterns. This case also further illustrates how gene-disease evidence mapping helps distinguish primary disease causing genes from secondary or modifying variants.

In silico structural interpretation of selected missense and truncating variants

In selected cases, protein structural modelling was performed to visualise the predicted impact of clinically relevant variants on protein architecture and domain integrity **(Supplementary Figures S1–S4)**. AlphaFold-based predictions were used to generate wild-type and mutant protein structures, which were visualised and compared using PyMOL. Structural modelling served as supportive context alongside clinical correlation and standard variant interpretation and was not used as standalone evidence for pathogenicity.

To provide supportive structural context for the developmental eye phenotype in Case 2, protein modelling of VSX2 was performed for the wild-type sequence and the predicted truncated product of the c.589C>T (p.Gln197Ter) variant. The wild-type model

demonstrates an N-terminal homeobox DNA-binding domain followed by a C-terminal region involved in transcriptional regulation, whereas the p.Gln197Ter variant is predicted to result in premature truncation with loss of the downstream C-terminal region while preserving the homeobox domain (Figure 3a, 3b) . Model confidence and internal consistency was assessed using per-residue pLDDT scores and predicted aligned error (PAE) plots **(Supplementary Figures S1 and S2)**.

For Case 3, structural modelling of CNGA3 was performed for the wild-type protein and the p.Arg436Trp variant to examine the local structural context of residue 436. Superposition of the models shows that the variant lies within a structured region of the predicted protein, allowing visualisation of the altered residue environment (Figure 3a, 3b). Model confidence was similarly assessed using pLDDT and PAE metrics **(Supplementary Figures S3 and S4)**.

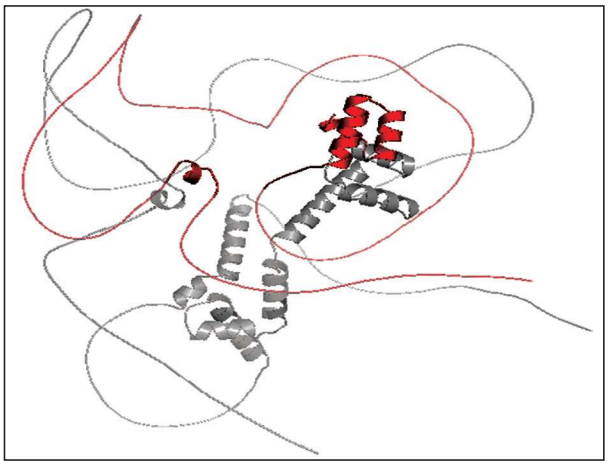


Figure 3a

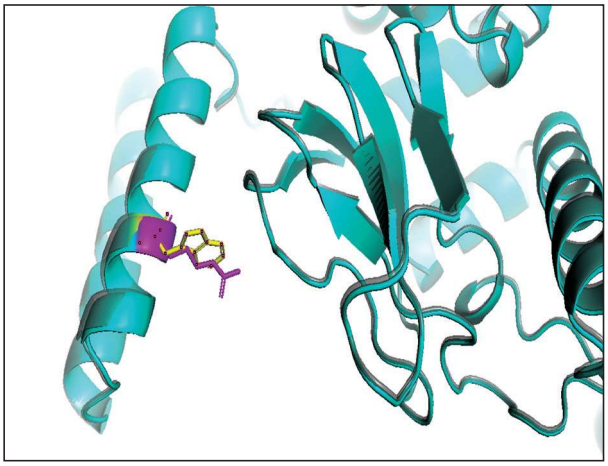


Figure 3b

Figure 3: Structural modeling and overlay analysis of VSX2 and CNGA3

(A) Overlay of the predicted three-dimensional structures of wild-type (WT) VSX2 and the truncated protein resulting from the c.589C>T (p.Gln197Ter) variant. The truncating variant leads to loss of the C-terminal region while preserving the N-terminal homeobox domain. The overlay highlights the extent of structural loss associated with the premature termination.

(B) Structural overlay of wild-type and mutant CNGA3 models based on the cryo-EM structure of human CNGA3 (PDB ID: 8EUC). The WT structure is shown in cyan, and the mutant model is shown in grey. Residue Arg436 in the WT protein is depicted as magenta sticks, while the substituted Trp436 in the mutant is shown as yellow sticks. The p.Arg436Trp substitution is located within an α-helical transmembrane region and represents replacement of a positively charged residue with a bulky hydrophobic side chain, suggesting disruption of local structural packing within the helix.

In both cases, structural modelling was used to visualise domain loss or local structural context and was interpreted alongside clinical findings, inheritance patterns, and established gene–disease evidence; it was not used as standalone evidence for variant classification. **(Supplementary: Methodological pipeline for structural modelling)**

Challenges and Solutions

Genetic ophthalmological disorders face distinct limitations of clinical complexity, technological advancement, and healthcare system, which need integration of genomics, genetic counseling, and multidisciplinary approach. In countries like India, the situation is further influenced by disparities in awareness, accessibility, and infrastructure, highlighting the need for targeted strategies in each of these areas.[56,59,60] Progress in molecular diagnostics, artificial intelligence, and collaborative care models shows great potential to improve

outcomes, but lasting impact will depend on coordinated efforts among clinicians, research persons, and policy makers.[61] Recognizing specific technical challenges of NGS such as failure to detect a mutation due to incomplete sequencing of a gene, mutation in the gene's promoter region, deletion of the entire gene, or mutation in another gene, is crucial for evaluating its effectiveness and addressing gaps in clinical practice.[46] Figure 4 below summarizes key challenges encountered in this domain alongside practical solutions aimed at bridging these gaps and advancing patient care (Figure 4a, b).[36,32,62,63,64]

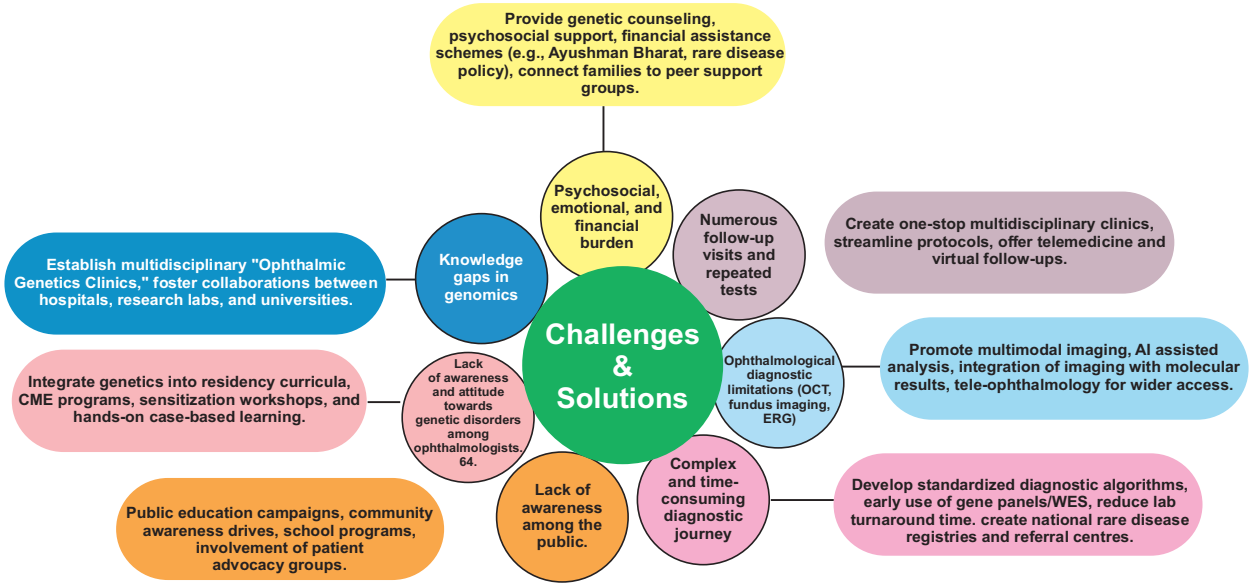


Figure 4a



Figure 4b

Figure 4 a **& b:** Challenges and Solutions in Genetic ophthalmological Disorders for integration of genetics into ophthalmology through collaboration, AI, education, standardized diagnostics, and patient support

Future Directions in Ophthalmic Genetics

Understanding the intricate relationship between genetics and ophthalmology underscores the importance of integrating NGS into routine clinical practice and adopting a multidisciplinary approach to patient care. Although genomics is rapidly approaching its full potential, its continued success will depend on nurturing a new generation of genomics-trained clinicians and researchers.

Being ophthalmic genetics has emerged as a vital subspecialty, there is a growing recognition of the need for structured post-residency fellowships, mentorship programs, and dual-training pathways that integrate ophthalmology with clinical or molecular genetics, as promoted by leading academic institutions and global experts.[66,67,68] The establishment of dedicated programs, societies, and publications in India and worldwide has strengthened clinical–genomic collaborations, refined genotype–phenotype correlations, and fostered high-impact multicentre studies.[69]

Ophthalmologists can now pursue specialized training through ophthalmic genetics fellowships, ACGME-accredited medical genetics residencies, or rotational programs that offer exposure to both pediatric and adult genetic disorders under expert supervision. Conversely, geneticists undertaking ophthalmology-focused training enhance diagnostic accuracy, prognostic evaluation, and patient counselling. Continued emphasis on education and clinician–scientist training will be essential to sustain progress in this field.

Recent breakthroughs in gene- and cell-based therapies are redefining the therapeutic landscape for inherited retinal diseases. The approval of gene therapy for RPE65-associated retinal dystrophy marks a milestone in precision ophthalmology.[70,55] Emerging technologies such as nanotechnology for targeted ocular drug delivery, stem-cell–based regenerative approaches, and gene-editing platforms like CRISPR/Cas9 hold tremendous promise for correcting pathogenic variants *in vivo*.[71,72] Together, these innovations, continues fall of sequencing cost and bioinformatics tools advancements, underscore the transformative potential of integrating genomics, cell biologists, bioinformaticians, molecular therapeutics, and clinical expertise to meet the growing global demand for precision eye care.

CONCLUSION

The evolving landscape of genetic ophthalmological disorders underscores the necessity to integrate clinical, technological, and policy-driven approaches for better understanding of genotypic-phenotypic correlations. Standard gene-disease evidence mapping, alongside variant interpretation is essential to prevent misdiagnosis and to translate genomic findings into meaningful clinical care. Systematic incorporation of genomic diagnostics, capacity building for clinicians, and development of collaborative care systems are key steps to address current gaps. Furthermore, stronger national registries, global partnerships, and equitable access to emerging therapies will be essential to bring precision medicine in ophthalmic genetics practice. Ultimately, building basic knowledge of ophthalmic genetics among doctors, sustained investment in research, education, and infrastructure will ensure that scientific progress leads to tangible benefits for patients and their families.

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