Review Article

Advances in retina genetics: Progress, potential, and challenges

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The field of retinal genetics has seen remarkable advancements lately, reshaping our understanding of various retinal conditions, including age-related macular degeneration, diabetic retinopathy, and inherited retinal dystrophies. The purpose of this review is to provide an overview of the current status of genetics in the retina, covering the progress made, the expected future developments, and the challenges yet to be overcome. We highlight key advancements such as the advent of next-generation sequencing, which has exponentially enhanced the discovery of genetic mutations, thus also enabling personalized medicine/therapeutic approaches. Stem cells, gene augmentation, and gene-editing techniques such as CRISPR/Cas9 are discussed, in which we highlight ongoing research as well as their potential in the targeted treatment of retinal diseases. Despite these promising advancements, the field faces significant challenges, such as the complex interpretation of genetic data, ethical considerations, and the translational gap from bench to bedside. This review serves as a comprehensive guide not only to ophthalmologists but also to other healthcare professionals, scientists, and policymakers, providing insights into the rapidly evolving landscape of retinal genetics. It aims to stimulate further research and collaboration to surmount existing challenges and harness the full potential of genetic advancements for retinal health.

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The convergence of the fields of genetics and ophthalmology is happening like never before. Advances in genetics and molecular biology are offering unprecedented insight into the retinal physiology and pathways affecting retinal disorders, thus subsequently giving us insight into therapeutic targets. From genetic testing to gene therapy, the landscape of retinal science is rapidly evolving. While the topic is vast, this article aims to provide an overview of the current status of genetics in the study and treatment of retinal disorders, including age-related macular degeneration (AMD), diabetic retinopathy (DR), and inherited retinal dystrophies (IRDs).

With access to next-generation sequencing (NGS), advances in stem cell research, refinement in viral vectors for delivery, the advent of technologies such as clustered regularly interspaced short palindromic repeats (CRISPR), and advances in bioinformatics, researchers can identify genetic markers and develop therapies to target these conditions.

Specifically, treatment for wet AMD has seen the advent of the U.S. Food and Drug Administration (FDA) approval of gene therapy for vascular endothelial growth factor (VEGF) inhibition (RGX-314). Treatment for dry AMD, on the contrary, has seen advancements with the development of stem cell-based therapies and complement factor inhibition by using RNA aptamer (avacincaptad pegol) or peptide-based inhibition (pegcetacoplan).[1] New treatments for DR are being developed, such as anti-VEGF gene therapies, receptor tyrosine kinase inhibitors, inhibitors of the angiopoietin-Tie2 pathway, and integrin pathway inhibitors.[2] The FDA approval of voretigene neparvovec in 2017 for *RPE65*-associated IRD has fueled research and development of gene therapies for various IRDs and are in different stages of clinical trials.[3] We aim to delve into the abovementioned areas in this review article and review and summarize the same.

Diagnostics

Identification of genetic factors

The evolution of genetic sequencing from Sanger sequencing to NGS more recently has facilitated large-scale genomic studies, personalized medicine initiatives, and a deeper understanding of genetic contributions to health and disease.[4] NGS has enabled faster, more cost-effective, and high-throughput sequencing.

These advances have facilitated the conducting of genome-wide association studies (GWAS), which have been instrumental in identifying genetic factors associated with AMD. Specifically, in a study involving a genome-wide screening of 96 individuals with AMD and 50 controls searching for genetic markers linked to the disease, out of

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116,204 single-nucleotide changes analyzed, a particular genetic variation inside the complement factor H gene (*CFH*) exhibited a strong correlation with AMD. These genetic markers have provided new insights into the underlying mechanisms of AMD and have opened up avenues for potential targeted therapies.[5]

GWAS have also played a vital role in unraveling the genetic landscape of DR. A variety of genes have been implicated in DR susceptibility, including genes associated with inflammation, angiogenesis, and oxidative stress. Some of the key genes that have been associated with DR through GWAS include *MRPL19* and *NRXN3* as new genetic locations tentatively linked to DME and PDR, respectively. In addition, it has been implicated that loci in *PCKS2* and *MALRD1* genes are causative in DR.[6] Furthermore, a study from India reported an association between genetic variation in the aldose reductase gene (A*KR1B1*) polymorphism -106C>T (rs759853) and DR.[7]

The identification of these causative genes has tremendous implications for both the prevention and treatment of DR. Understanding the role of *VEGFA*, for instance, has led to therapies targeting VEGF, which have shown considerable promise in treating DR. Similarly, knowledge about the *AKR1B1* gene, implicated in oxidative stress pathways, could lead to the development of targeted antioxidant therapies. The findings from GWAS offer the potential for personalized treatment plans tailored to an individual's genetic makeup, which could more effectively prevent the progression of DR or even reverse its effects. The challenge now lies in translating these genetic discoveries into clinical practice, a task that will likely involve a multidisciplinary approach integrating genomics, bioinformatics, and clinical ophthalmology.

The sheer volume of data generated can be overwhelming and requires sophisticated bioinformatics tools for interpretation. Moreover, the technology is sensitive to errors in the form of false positives and negatives, which can be critical when identifying pathogenic mutations. The reports generated generally mention the genetic variant to be either pathogenic, likely pathogenic, or variations of uncertain significance (VUS). All of these are determined based on comparison with previous published literature, reference databases, and American College of Medical Genetics guidelines.[8] At this point, meaningful interpretation of the report by the geneticist, retina specialist, correlating family history, and phenotype is important. Especially in cases of VUS, further testing may or may not be needed. Genetic testing is not just for diagnosis but also for genetic counseling and family planning, in addition to prognostic assessment, helping clinicians predict the likely course of a disease, and discussing prognosis with patients accordingly.

Therapeutics

Cell-based therapy

Stem cell-based therapies are increasingly being viewed as a promising frontier in treating degenerative retinal diseases such as dry AMD and IRDs. Human embryonic stem cells (hESCs) derived retinal pigment epithelium (RPE) in clinical trials, wherein a suspension of cells was delivered in the subretinal space, with an improvement in visual acuity reported in ten patients.[9] However, the use of hESCs raised ethical concerns. It has also been found that various stem cells, such as those from adipose tissue, bone marrow, and umbilical mesenchymal stem cells (MSCs), can produce versatile exosomes with minimal toxicity and immunological reactions. While MSCs act via paracrine mechanisms, there is limited evidence for their ability to replace damaged cells.[10] Furthermore, MSCs primarily differentiate into tissues derived from mesoderm, significantly different from the retina, limiting their functionality.[11]

With the advent of induced pluripotent stem cells (iPSCs)[12] from patient skin fibroblasts and peripheral blood mononuclear cells (PBMCs), which circumvented the need for human embryos, recent research has focused on iPSCs. These iPSCs can be programmed to differentiate into RPE cells and can be delivered over a scaffold[13] or injected in the subretinal space.[14] While delivering over a scaffold is technically challenging, it reduces the chances of efflux of cells and the development of epiretinal membrane.[15] In addition, iPSC-derived 3D retinal organoids and photoreceptor progenitor cells are being developed, which hold potential for regenerative cell therapies.[16]

While early-phase trials have indicated both a favorable safety profile and some functional benefits, a range of challenges persists. These include optimizing the differentiation process to yield high-quality retinal cells, ensuring the long-term survival and integration of these cells into the host tissue, and addressing ethical concerns related to the use of certain types of stem cells.[17]

Gene therapy for IRDs

In 2017, voretigene neparvovec received approval from the U.S. FDA for the treatment of IRD due to biallelic mutations in the retinal-pigmented epithelium 65 (*RPE65*) gene. Subsequently, many gene therapy clinical trials are ongoing [Table 1], addressing various forms of IRDs. Particularly noteworthy is the growing emphasis on targeting *RPGR* for X-linked retinitis pigmentosa and *ABCA4* for Stargardt disease. Among delivery mechanisms, adeno-associated virus (AAV) vectors continue to dominate due to their low immunogenicity and proven efficacy.[18] Gene therapy, also called gene augmentation therapy, essentially consists of delivering a wild-type copy of the gene of interest via a viral vector. After injection, the viral vector binds the capsid to the host cell and delivers the DNA payload into the cell, where it is translated into a protein through the cellular molecular machinery.

While currently there is an extensive list of gene therapies in clinical trials worldwide, Table 2 gives a summary[19]:

Table 1: This table summarizes the types of cell-based therapies being researched for various eye conditions, specifically age-related macular degeneration (AMD) and inherited retinal dystrophies (IRDs), along with their stages in clinical trials

Cell-Based Therapies (Cell Type)	Progress
AMD-dry, GA (RPE) – Astellas	Phase 1/2
AMD-dry, GA (RPE) – Lineage	Phase 1/2
AMD-dry, GA (RPE) – Luxa	Phase 1/2
AMD-dry, GA (RPE from iPSC) – NEI	Phase 1/2
AMD-dry, GA (RPE on scaffold) – Regen Patch	Phase 1/2
IRD, Usher (retinal progenitors) – jCyte	Phase 2b

Gene therapy for Neovascular AMD and DR

Regenxbio Inc. is currently conducting two clinical trials, namely ALTITUDE (NCT04567550) and AAVIATE (NCT04514653), for their drug RGX-314, utilizing a newly developed and less invasive suprachoroidal injection procedure. RGX-314 is engineered as a singular gene therapy approach by utilizing an adeno-associated virus 8 (AAV8) vector. This vector is employed to administer an anti-VEGF fab transgene, with the aim of potentially generating sustained anti-VEGF therapy within the eye.

Preclinical investigations have demonstrated that suprachoroidal injections of RGX-314 exhibit a comparable level of efficacy in inhibiting vascular leakage when compared to traditional subretinal injections. These phase II clinical trials administer the gene therapy product RGX-314 to patients with DR and neovascular AMD (nAMD), respectively. Initial findings from the DR cohort, treated with 2.5×10^{11} vg, indicated no serious drug-related adverse events within the 3-month study period, and some patients displayed improvements in vision. Similarly, the nAMD group reported no serious adverse events in patients treated with 2.5×10^{11} and 5×10^{11} vg of RGX-314. At the 6-month follow-up, individuals treated with the 2.5×10^{11} vg dose exhibited stable visual acuity and retinal thickness.

Gene editing (CRISPR/Cas9)

While gene therapy, also known as gene augmentation therapy, involves providing the patient's cells with a healthy copy of the mutated gene, gene editing techniques utilize enzyme-based "molecular scissors" to surgically modify or correct the flawed gene responsible for the genetic mutation. Gene editing offers the advantage of precise customization of the genome, eliminating the need to continually supply the affected cells (or tissue/organ/organism) with a healthy gene copy, making it an especially suitable therapeutic approach. Gene therapy provides for a correct copy of the gene which is effective in autosomal recessive disorders, wherein the wild type or correct copy of the gene is able to supplement and generate enough correct protein load for cellular function. However, gene editing is a suitable strategy for all types of mutations, irrespective of the mode of inheritance.

The application of CRISPR gene editing in the field of ophthalmology holds tremendous promise, particularly for the treatment of retinal dystrophies. The foundation of the CRISPR-Cas9 system lies in bacterial defense mechanisms against invading viruses, typically referred to as bacteriophages. When a bacteriophage invades a bacteria, a fragment of the viral DNA integrates into the bacterial genome. Upon subsequent infections, the bacteria identify this viral genetic material, triggering an adaptive immune response orchestrated by various proteins found in the CRISPR locus, primarily composed of CRISPR-associated (Cas) proteins. This culminates in the cleavage of viral DNA, effectively shielding the bacteria from the invading pathogen.[20]

These characteristics of the CRISPR mechanism have been harnessed for therapeutic purposes. The Cas nuclease enzyme can also be employed to cleave non-viral DNA, including human cell DNA. Essentially, when the target gene region is identified, a single guide RNA (sgRNA) can be synthesized. This sgRNA is complementary to the target gene sequence and perfectly matches the non-target sequence. When combined with the Cas9 protein, it forms a Ribonucleoprotein complex (RNP) capable of homing in on the target and creating a double-strand DNA break.

Upon DNA breakage, the cell initiates DNA repair through one of two primary mechanisms: non-homologous end joining (NHEJ) or homology-directed repair (HDR). In NHEJ, the DNA ends are directly rejoined or ligated without relying on a homologous template, often resulting in errors during repair, including insertions or deletions. In contrast, HDR uses homologous sequences from a DNA template containing desired edits or inserts to repair the damage caused by the RNP-induced cleavage. This process facilitates the introduction of desired sequences, thereby rectifying mutations, modeling diseases, or tagging genes.

CRISPR Base Editors: The Cas endonuclease can undergo modification to eliminate cleavage activity, referred to as catalytically deactivated Cas (dCas). It can then be coupled with protein enzymatic domains capable of performing nucleotide conversions. This form of editing operates independently of double-strand DNA breaks or repair pathways and is known as base editing. The CRISPR RNP complex binds to the target DNA, and the nuclease Cas9, fused with a deaminase enzyme, facilitates the conversion of cytosine to thymine, resulting in the generation of a cytosine base editor (CBE). Similarly, adenine can be deaminated to guanine, creating an adenine base editor (ABE).

CRISPR-based editors offer several advantages. They are highly effective for addressing most genetic disorders characterized by transition point mutations.[21] A study examined genes that posed challenges for traditional gene therapy due to their large size and difficulties in AAV packaging. The analysis of genes such as *ABCA4, CDH23, CEP290, EYS, MYO7A,* and *USH2A* revealed that CRISPR-based editing could effectively correct most pathogenic variants.[22]

CRISPR Prime Editing: One of the latest advancements in the CRISPR toolkit is the introduction of CRISPR prime editing.[23] This innovative technique involves the utilization of the Cas9 enzyme with nickase capabilities (nCas9), in conjunction with a reverse transcriptase, a prime editor guide RNA (pegRNA) featuring a primer binding site (PBS), and a reverse transcriptase (RT) template RNA. Importantly, this technique facilitates genome modifications without the necessity for potentially harmful double-strand DNA breakage, making prime editing a versatile tool capable of addressing a wide array of mutation types.

CRISPR RNA Editing: RNA editing, as a technology, holds the capacity to modify gene expression by introducing alterations at the transcript level. This approach offers a notable safety advantage as RNA edits are transient when compared to permanent DNA genomic alterations. Researchers have explored this strategy for the editing of extensive genes such as *USH2A*.[24] In addition, this method has been evaluated in a mouse model of choroidal neovascularization (CNV) to modify the expression of *VEGF*.[25]

Limitations with CRISPR Genomic Editing:

i. Off-target effects
ii. Proximity of PAM sequences
iii. Challenges in vector packaging

Table 2: Summarizing gene therapies in retinal dystrophies

Gene Therapy Product	Company	Target Gene	Indication	Clinical Trial	Status	Key Findings
Botaretigene sparoparvovec (MGT009)	MeiraGTx/ Janssen	*RPGR*	X-linked RP (XLRP)	Phase 1/2 (NCT03252847)	Completed	Favorable safety; Improved retinal sensitivity in low- and intermediate-dose cohorts. Phase 3 trial LUMEOS (NCT04671433) actively recruiting.
Laruparetigene zosaparvovec (AGTC-501)	Beacon Therapeutics	*RPGR*	XLRP	Phase 1/2 SKYLINE (NCT03316560)	Completed	Improved microperimetry sensitivity in centrally dosed patients. Phase 2/3 study VISTA (NCT04850118) planned.
Cotoretigene toliparvovec (BIIB112)	Biogen	*RPGR*	XLRP	XIRIUS trial (NCT03116113)	Ongoing	Positive trends observed; Transition to phase 3 trial SOLSTICE (NCT03584165) for long-term monitoring.
4D-125	4D Molecular Therapeutics	*RPGR*	XLRP	Phase 1/2 EXCEL (NCT04517149)	Active	Received FDA fast-track designation.
AAV2/5-hPDE6B (CTx-PDE6b)	Coave Therapeutics	*PDE6b*	PDE6b-associated RP	Phase 1/2 (NCT03328130)	Ongoing	Preliminary positive efficacy in six patients with early disease.
SAR439483 (ATSN-101)	Atsena Therapeutics	*GUCY2D*	Leber Congenital Amaurosis (LCA1)	Phase 1/2	Ongoing	Preliminary 6-month data showed improved retinal sensitivity.
ATSN-201	Atsena Therapeutics	*RS1*	X-Linked Retinoschisis	Phase 1/2	FDA cleared for phase 1/2	Uses novel AAV.SPR capsid which spreads laterally beyond the subretinal bleb margin
Lenadogene nolparvovec (Lumevoq)	GenSight Biologics	MT-*ND4*	Leber Hereditary Optic Neuropathy	Phase 3 REFLECT (NCT03293524)	Completed	Clinically meaningful improvement in visual acuity; Well-tolerated with intraocular inflammation.
4D-110	4D Molecular Therapeutics	*CHM*	Choroideremia	Phase 1/2 (NCT04483440)	Active	Awaiting preliminary data in June 2024.

While CRISPR-Cas9 is an invaluable tool, it may inadvertently bind to genomic regions that exhibit some similarity to the target sequences, resulting in unintended genetic alterations known as off-target effects.

In addition, there are instances where the target mutation may be located in regions lacking the required Protospacer Adjacent Motif (PAM) sequences for optimal Cas9 activity. Researchers have experimented with engineering Cas9 enzymes to modify their PAM requirements to overcome this limitation.

The size of the Cas9 enzyme and the sgRNA may often exceed the AAV carrying capacity of 4.5 kbps. To mitigate this, other vectors, such as nanoparticles and liposomal delivery, are being explored.

Current status of CRISPR gene editing in the retina

Mutations occurring in the *CEP290* gene commonly result in early-onset vision impairment and retinal changes, often exhibiting a familial pattern. Due to the gene's substantial size, AAV vectors are insufficient for delivery, necessitating alternative methods such as CRISPR for potential therapeutic intervention. Specifically, a cryptic mutation within intron 26 (IVS26) of the *CEP290* gene has been detected, leading to an abnormal splice donor site and the formation of a premature truncation codon. Ruan *et al*.successfully showcased the editing of this site and IVS26 excision by using CRISPR technology, achieving an editing efficiency ranging from 59% to 69%.[26] Expanding on these findings, *in vivo* experiments were carried out in both a CEP290-IVS26 knock-in mouse model and a non-human primate (NHP) model. Encouraged by these results, a phase 1/2a clinical trial called "BRILLIANCE" was commenced. This trial involved subretinal injection of a CRISPR gene-editing treatment drug called EDIT-101, aiming to edit the c.2991 + 1655A>G mutation within intron 26 (IVS26) of the *CEP290* gene.[27]

Optogenetics

Optogenetics, in principle, is a neuromodulation technique that uses light to control neurons genetically modified to express a light-sensitive protein. This method circumvents the host's photoreceptors to activate the surviving inner retinal neurons and the pathways that follow them. Light-sensitive microbial opsin genes and proteins, such as channelrhodopsin and halorhodopsin, are delivered into bipolar or ganglion cells by using viral vectors, which then get activated on light exposure and generate a visual response.[28] Table 3 summarizes the list of ongoing trials.

Antisense oligonucleotides (AONs)

Antisense oligonucleotides (AON) refer to artificially created, single-stranded nucleic acid fragments designed to selectively bind to a specific complementary messenger RNA (mRNA) sequence, thereby influencing the ultimate gene product. Initially approved for the treatment of cytomegalovirus retinitis, AON has demonstrated potential in addressing Mendelian systemic diseases. Ongoing research is exploring the utility of AON as a therapeutic approach for various ophthalmic conditions, encompassing inherited retinal disorders (IRD), inflammatory responses, wound healing following glaucoma

Table 3: List of ongoing optogenetics gene therapy trials

Gene Therapy Product	Company	Target Mechanism	Indication	Clinical Trial	Status	Key Findings
Sonpiretigene isteparvovec (MCO-010)	Nanoscope Therapeutics	Opsin expression to bipolar cells	NA	Phase 1/2 (NCT04919473)	Completed	Demonstrated safety; Improved vision-guided mobility. Phase 2 trial RESTORE (NCT04945772) ongoing.
GS030	Gensight Biologics	AAV2-based gene therapy with light-stimulating goggles	End-stage RP	Preliminary data	Ongoing	Improved object localization and counting observed 1 year after treatment.
BS01	Bionic Sight	Recombinant AAV vector with enhanced light-sensitive channelrhodopsin gene	RP	Phase 1/2 (NCT04278131)	Ongoing	Promising interim data with improved object recognition.

surgery, and macular degeneration. Notably, AON presents a viable alternative for gene therapy in cases of IRD where AAV delivery is not a feasible option.[29] QR-421a (ProQR Therapeutics) is in phase 1/2 trial STELLAR (NCT05176717) for patients with Usher syndrome. Preliminary data has shown improved visual acuity and retinal sensitivity.

Challenges

Cost of therapy

The pursuit of gene therapy for retinal disorders presents significant challenges, particularly pertaining to cost. The development and implementation of gene therapies entail the development and maintenance of strictly regulated facilities. This is further compounded by the intricacies of targeting specific genes contributing to the overall financial burden. Production of viral vectors for delivery, gene editing tools, and ensuring the safety and efficacy of these therapies incur substantial costs. In addition, conducting clinical trials, seeking regulatory approvals, and ongoing monitoring further increase the expenses. As these therapies hold promise for addressing progressively blinding conditions, finding a balance between affordability and accessibility for most individuals will be crucial to ensure broader patient access. Efforts to streamline the production processes, enhance efficiency, and explore reimbursement strategies will be critical steps toward making gene therapies for retinal disorders a more financially sustainable and accessible therapeutic option.

Monitoring response to treatment

Monitoring the response to gene therapy for retinal disorders introduces distinct challenges, particularly in the context of documenting non-progression of the disease as mostly gene augmentation and editing therapies have a role in halting progression. The conventional methods of assessing treatment efficacy, such as visual acuity measurements and structural imaging, may not adequately capture the intricacies of retinal changes at the genetic level. In addition, the longitudinal nature of monitoring response in gene therapy requires sustained efforts and resources, demanding a comprehensive approach that includes both functional and anatomical assessments. The lack of established biomarkers for certain retinal disorders further complicates the evaluation process. While the multi-luminance mobility test (MLMT) was primarily developed for this purpose, the feasibility of replicating it at eye treatment facilities remains a challenge. A surrogate test, the full field stimulus testing or FST has been used instead to monitor response to treatment.

Future directions

Advancements in genetic sequencing combined with advances in artificial intelligence (AI) and bioinformatics are expected to play a significant role in analyzing genetic data to pinpoint causal factors for retinal diseases. Collaborative efforts, such as the Human Cell Atlas, aim to map every cell in the human body, offering enormous potential for understanding retinal diseases on a cellular level.[30]

Conclusion

The field of genetics is dramatically reshaping our understanding and treatment of retinal diseases. While challenges such as ethical considerations and limited accessibility remain, the future holds promise for more effective and personalized treatments for a wide range of retinal disorders. As science and technology continue to advance, we can expect even more groundbreaking developments that bring us closer to comprehensive solutions for retinal health.

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