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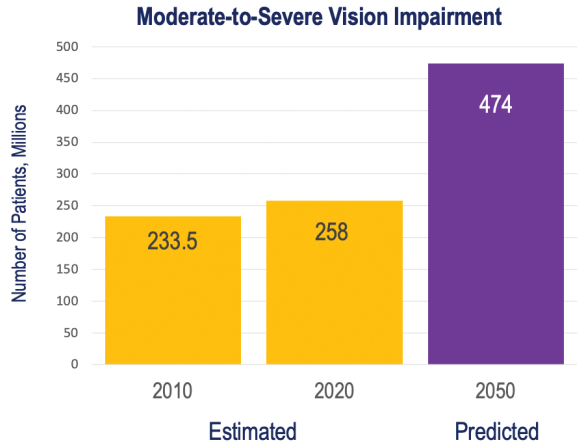
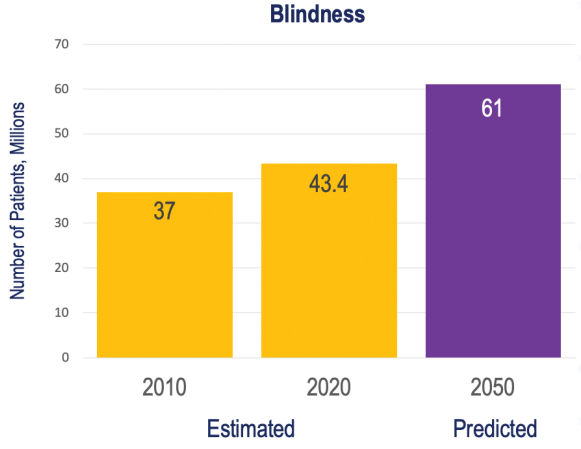
Increased Needs and Therapeutic Opportunities for Inherited Retinal Diseases

Vision Loss to Increase Globally Through 2050

Globally, in 2010, an estimated 37 million people were blind and an additional 233.5 million people had moderate-to-severe vision impairment. In 2020, 258 million people were estimated to have mild vision impairment, 295 million people were estimated to have moderate-to-severe visual impairment, and 43.4 million people were estimated to be blind worldwide.[1] Altogether by 2050, mild vision impairment is predicted to affect 360 million people altogether, moderate-to-severe vision impairment is predicted to affect 474 million people, and the number of people with blindness in the global population is predicted to increase to 61 million.[1] Between 2020 and 2050, the proportion of the world's population aged 65 years or older is expected to double, from approximately 1 billion to 2 billion.[2] As vision loss increases globally through the year 2020, the aging of the world's population will have critical ramifications on age-related diseases, including age-related blindness.[1] Therefore, the large burden of mild vision impairment, moderate-to-severe vision impairment, and blindness may become overwhelming as the global population continues to age through 2050.[1]

Increase in Moderate-to-Severe Vision Impairment and Blindness: 2010 through 2050





Genetic Basis of Visual Impairment and Blindness

Human genes contain all the information regarding body development and functioning.[3] One malfunctioning gene can cause abnormal body development which may result in a serious disease.[3] Such conditions that are caused by gene error and passed down hereditarily are distinguished as hereditary diseases or disorders.[3] In the case of the eye, such ocular disorders are described as genetic eye diseases or inherited retinal diseases.[3] Approximately one in 2,000 people worldwide are affected with inherited retinal diseases.[4] In fact, around one-third of cases of blindness or severe visual impairment have a genetic basis, either as part of a multifactorial etiology or as the direct result of genetic mutations, such as is the case in inherited retinal diseases.[5,6] There are more than 350 genetic eye diseases that impact individuals of all ages, encompass a broad spectrum of disease, and can affect all parts of the eye.[3,5] Inherited retinal disorders are a broad group of genetic nonprogressive and progressive sight loss disorders characterized by retinal degeneration.[5] Included among these many disorders are Leber's congenital amaurosis, severe early onset retinal dystrophies, congenital stationary night blindness, achromatopsia, cone and rod dystrophies, retinitis pigmentosa, and macular dystrophies.[6] Characteristically, the impaired vision in inherited retinal diseases is due to retinal photoreceptor dysfunction and loss resulting from mutation in a gene that codes for a retinal protein.[6] For example, *RPE65* mutations are responsible for Leber's congenital amaurosis.[7-10] In addition, there are six phototransduction genes known to be implicated in achromatopsia, with loss-of-function mutations in *CNGA3* and *CNGB3* accounting for greater than 70% of cases.[11,12] Choroideremia is caused by mutations or deletions in the gene, *CHM*, an encoder of the intracellular trafficker Rab escort protein-1 (REP1).[13] Autosomal recessive Stargardt disease is caused by mutations in *ABCA4*, an encoder of a photoreceptor ATP-binding cassette transporter.[14] Over 67 causative genes with many disease-causing variants have been identified in association with retinitis pigmentosa.[15] X-linked retinitis pigmentosa is most commonly caused by mutations in the retinitis pigmentosa GTPase regulator (*RPGR*) gene.[16] Mitochondrial DNA point mutations in the nicotinamide adenine dinucleotide dehydrogenase subunit 4 (ND4) are responsible for a majority of Leber's hereditary optic neuropathy cases.[17] X-linked juvenile retinoschisis is caused by mutations in the gene retinoschisin 1 (*RS1*), an encoder of retinoschisin, a secretory protein essential for retinal organization and intracellular adhesion.[18]

> There are more than 350 genetic eye diseases that impact individuals of all ages, encompass a broad spectrum of disease, and can affect all parts of the eye.

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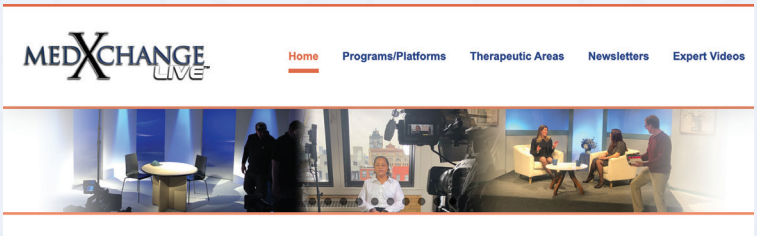

THEIR GENES GAVE THEM BUTTON NOSES, BROWN HAIR, AND VISION LOSS

To date, science has discovered more than 270 genes related to **inherited retinal diseases**.[1] With the evolution of genetic testing comes the ability to more precisely diagnose your patients.

More answers may uncover more possibilities for active clinical trials, emerging treatments, and even identifying underlying conditions beyond vision issues.

MOVE FORWARD WITH MORE ANSWERS

Scan to find more answers about genetic testing and retesting at **EyesOnGenes.com**.

Reference: 1. Branham K, Schlegel D, Fahim AT, Jayasundera KT. Genetic testing for inherited retinal degenerations: triumphs and tribulations. *Am J Med Genet C Semin Med Genet.* 2020;184(3):571-577.

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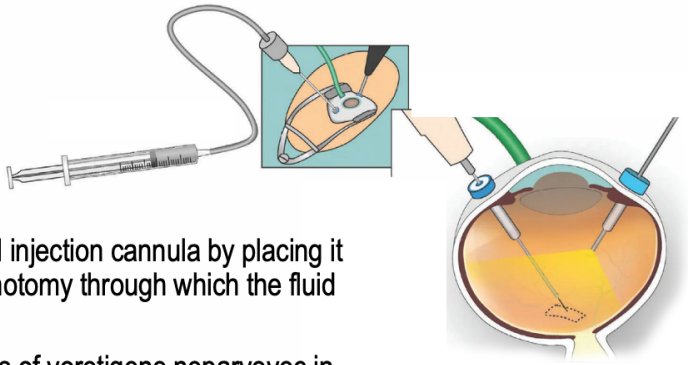
Gene Therapy and *RPE65*-associated Leber Congenital Amaurosis

RPE65-linked inherited retinal disease typically manifests as Leber congenital amaurosis, which is characterized by severe visual impairment from birth or early infancy with light staring and profound nyctalopia accompanied by nystagmus and poor pupillary light responses.[23] Treatment of autosomal recessive disease is intuitive in the sense that replacement of the defective gene with a functional copy should ameliorate disease, and this approach has already been applied with success for *RPE65* mutations responsible for Leber's congenital amaurosis, the first inherited retinal disease to be explored for gene therapy.[10,24,25] Until the advent of *RPE65* gene therapy, the disease naturally progressed to legal blindness.[26] In December 2017, following the successful randomized, controlled, open-label, phase 3 trial, voretigene neparvovec (Luxturna) became the first ocular gene therapy approved for *RPE65*-associated retinal dystrophy.[10,,27,29] Voretigene neparvovec consists of the capsid of an adeno-associated viral vector serotype 2 (AAV2) containing a correct coding sequence (cDNA) of the human *RPE65* gene and regulatory elements.[28,29] The one-time gene therapy aims to deliver the correct coding sequence of the human *RPE65* gene to the retinal pigment epithelium and is performed via subretinal injection following vitrectomy.[28,29] Once in the nucleus, the single-stranded DNA is transcribed into double-stranded DNA, and the mRNA is subsequently translated in the cytosol into the functional protein, the enzyme isomerohydrolase.[28,29]

- Voretigene neparvovec is provided in the form of frozen concentrate
- A syringe contains the vector solution
- Vector solution must be applied within 4 hours after preparation
- Following vitrectomy, vector solution is delivered via a small injection cannula by placing it onto the retina and applying slight pressure to create a retinotomy through which the fluid can pass into the subretinal space
- Patients receive a single dose of 1.5 x 1011 vector genomes of voretigene neparvovec in each eye



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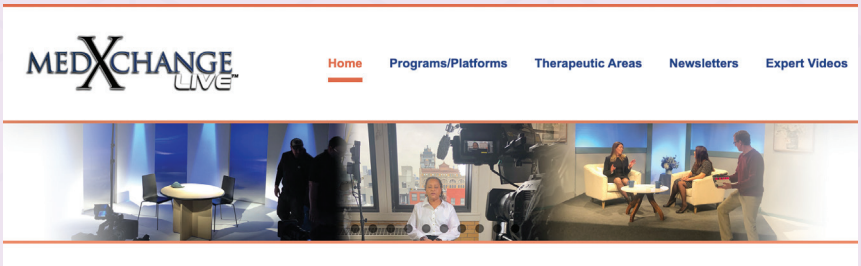


Therapies in Development for Inherited Retinal Disorders

Inherited retinal disorders are a genetically and phenotypically heterogeneous group of genetic eye disorders.[6] There are greater than 300 disease entities, and together this group of disorders affects at least 1 in 1400 individuals, or around 5.5 million people worldwide.[30,31] However, each type of inherited retinal disorder is rare or ultra-rare.[6] Voretigene neparvovec (Luxturna) was the first ocular gene therapy approved for RPE65-associated retinal dystrophy.[10,27,29] Since the approval of voretigene neparvovec, there has been a worldwide research effort surrounding retinal gene therapy for various other monogenic inherited retinal diseases to identify the optimal gene therapy approaches.[10,32] Disorders being targeted for genetic therapy include retinitis pigmentosa, Leber congenital amaurosis, choroideremia, achromatopsia, Leber's hereditary optic neuropathy, X-linked retinoschisis, and Stargardt disease.[33] In addition to different types of gene therapy, there are several other therapies in development for the treatment of inherited retinal disorders, including cell therapy, visual prosthetics, optogenetics, and RNA-based therapies.[34,35]

Additional gene-based therapies that are different than gene replacement using adeno-associated virus (AAV) and nonviral delivery vectors seen with voretigene neparvovec but also have the potential to treat inherited retinal diseases are being studied.[36] These include genome editing via the CRISPR/Cas9 system.[36]

Cell therapy for inherited retinal diseases includes the introduction of stem cells to replace degenerated cells through delivery to target tissues (i.e., photoreceptors and retinal pigment epithelium).[37] Cell therapies are expected to slow disease progression and restore some visual functions, but there are several limitations to such therapies.[37]

Retinal prostheses are implantable devices that aim to restore the vision of blind patients suffering from retinal degeneration, mainly by artificially stimulating the remaining retinal neurons.[38] Some retinal prostheses have successfully reached the stage of clinical trials; however, these devices can only restore vision partially.[38]

Optogenetics are primarily aimed at rendering secondary and tertiary neurons of the retina light-sensitive in order to replace degenerate or dysfunctional photoreceptors.[39] Optogenetic approaches provide a causative gene-independent strategy, which may prove suitable for a variety of patients with inherited retinal disease.[39] Optogenetic approaches to vision restoration yielded promising results in preclinical trials.[39]

RNA-based therapies are a novel approach within precision medicine that have demonstrated success, particularly in rare diseases.[6] Three antisense oligonucleotides are currently in development for the treatment of specific inherited retinal diseases.[6] These RNA-based therapies have the potential to bring meaningful vision benefit to people living with inherited retinal diseases that can lead to blindness.[6]

RNA-based Therapy for Inherited Retinal Disorders

The retina has historically played an important role in RNA-based therapy development, with an approval for an antisense oligonucleotide (ASO) in 1998 for the treatment of cytomegalovirus retinitis.[47] Inherited retinal dystrophies are one such category of diseases that have shown significant advancement in treatment strategies, namely following the approval of the first gene therapy for a genetic disease in 2017 (voretigene neparvovec).[10,27,29] RNA-based therapies are an innovative approach within precision medicine that offers some specific key advantages in the setting of inherited retinal diseases, and the potential to bring meaningful vision benefit to individuals living with these inherited blinding disorders.[6] Three ASO therapies are in clinical trials in specific inherited retinal diseases with early promising data.[6,48] These therapies in development are targeting disease mutations which result in splicing defects.[48] One experimental drug has demonstrated promising results in a phase I/II clinical trial in patients with Leber's congenital amaurosis 10.[48,49] This novel therapy is an ASO that targets the p.Cys998X mutation in the CEP290 gene, which results in aberrant splicing with resulting premature stop codon, a frequent cause of Leber's congenital amaurosis ciliopathies and has demonstrated vision improvement after 12 months of treatment in a recent trial.[49] Many RNA-based therapies can be administered intravitreally and have the potential for a pan-retinal effect.[48] However, RNA-based therapies are generally mutation-specific and may require repeat administration.[48]

Differences Between DNA-based Gene Therapy and RNA-based Therapy

The treatment paradigm for genetic eye diseases is in the midst of great change, driven by advances in knowledge of the diseases and innovations in therapeutic technologies.[6] Gene therapies are a one-time, potentially life-changing, DNA-based treatment that can provide a durable and potentially curative clinical benefit for a diverse range of diseases, including inherited retinal diseases.[32,40] Gene therapy offers a theoretical advantage over small molecules classically used as medicines.[32] Gene therapies function via several mechanisms, such as replacing a disease-causing gene with a healthy copy, inactivating a disease-causing gene, or introducing a new or modified gene to treat a disease.[41] Since inherited retinal diseases are a heterogenous group of orphan eye diseases that typically result from monogenic mutations, they are considered attractive targets for gene therapies.[36] Therefore, although historically limited by their previously incurable nature, the retina has been thoroughly investigated over the past two decades for gene therapy interventions for inherited retinal diseases because it is immune-privileged, enclosed, and easily monitored.[42] Voretigene neparvovec was the first ocular gene therapy approved for RPE65-associated retinal dystrophy.[10,27,29] Following the historic approval of this inherited retinal disease gene replacement therapy for Leber's congenital amaurosis due to *RPE65* mutations, there has been a worldwide research effort surrounding retinal gene therapy for various other monogenic inherited retinal diseases to identify the optimal gene therapy approaches.[10,32] The ability of gene therapies to provide durable health benefits for patients with inherited retinal diseases justifies the continued optimism and increasing efforts towards making gene therapy part of the available standard treatments in ophthalmology, due to the clear advantages of the eye as being a compartmentalized, small, immune-privileged structure.[32] RNA therapies can be considered a form of genetic therapy as they are highly specific and target the underlying genetic cause of a disease,[43-46] but RNA-based therapy and DNA-based therapy (gene therapy), are two different approaches.[45] RNA- and DNA-based therapies differ in several ways including mechanism of action, permanency of effect, and delivery to the target cells.[45,46] The key differences between RNA- and DNA-based therapy in the setting of inherited retinal diseases include RNAs act at the RNA level and do not alter the genome, RNAs have long-lasting effect but not permanent effects, RNAs do not require vectors for delivery, and RNAs are administered via intravitreal injection.[6] Although there is one gene therapy approved for treatment, there are currently no approved RNA-based therapies for inherited retinal diseases.[6] Three investigational RNA-based therapies for inherited retinal diseases are in clinical trials.[6]

Key Differentiating Features: Gene-based Therapies and RNA Therapies

Gene-based Therapies	RNA Therapies
• Target the DNA	• Act at the level of the RNA
• Can directly alter the genome	• Do not alter DNA
• Induces double-strand breaks	• No double-strand breaks generation
• Potential for single treatment/dosing	• Requires repeat dosing
• Require viral vectors for delivery	• Naked, no vectors needed
• Usually limited to diseases with small gene size	• Can target diseases with large, affected genes
• Usually require subretinal administration; surgery involves vitrectomy	• Can be administered via routine intravitreal injection

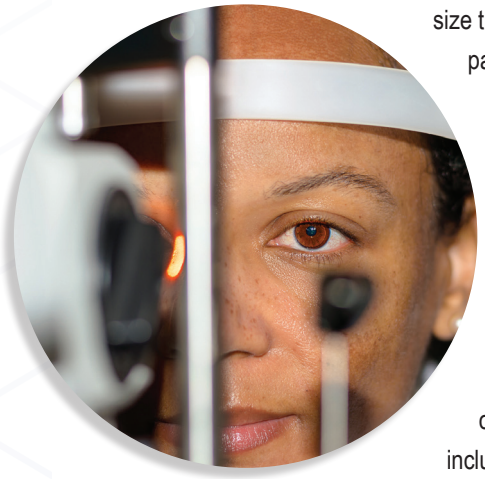
Early and Accurate Diagnosis with Genetic Screening Can Optimize Outcomes

Historically, the management of inherited retinal diseases has involved obtaining clinical genetic testing only if available, offering genetic counseling, and managing symptoms and complications.[50] Recently, interest in genetic testing has increased dramatically as a result of a newly available gene therapy (voretigene neparvovec, an *RPE65* gene therapy) and other emerging gene therapies in clinical trials.[50] However, genetic testing is not routinely performed, in part because of insufficient access, the impracticality of testing, and the lack of understanding the diagnostic value of testing.[50] An early and accurate diagnosis with genetic testing can help predict vision loss and help establish a treatment plan.[50,51] Patients with inherited retinal diseases can present with visual impairment at any age.[10] The timing and circumstances surrounding the loss of photoreceptor function determine the adequate therapeutic approach to use for each patient.[10,36] Some progressive inherited retinal diseases have a large window of opportunity where interventions can be made resulting in potentially lifetime benefit.[36] Results from clinical studies determining the benefits of early treatment for patients with inherited retinal diseases emphasize the need for access to genetic screening to identify patients who might benefit from gene therapy.[10]

> An early and accurate diagnosis with genetic testing can help predict vision loss and help establish a treatment plan.

Genetic Testing Can Assist to:

- Provide accurate diagnosis
- Identify optimal precision treatment
- Detect inheritance risk information
- Improve genetic counseling
- Identify clinical trials for participation

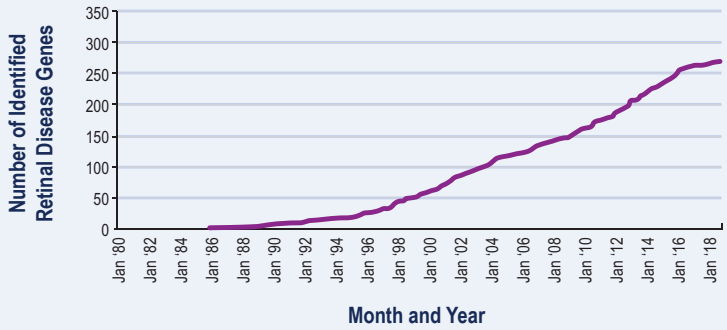


Genetic testing is rapidly advancing in inherited retinal diseases as a result of the increasing potential for treatment with gene therapy.[50-53] Therefore, genetic testing is now recommended as an important component in the diagnosis and management of inherited retinal diseases.[52,53] The first part of clinical, genetic testing is determining if there is likely an inherited retinal disease and determining the differential diagnosis.[52,53] Next, the selected panel should be checked to include the genes known to be associated with the differential diagnoses.[50-53] Results from genetic testing can provide an accurate diagnosis that may assist in identifying an available optimal treatment.[53] Successful genetic testing can have other benefits in addition to providing precise diagnostic information, including detecting valuable inheritance risk information.[52] Accurate identification of the inheritance pattern through genetic testing may improve genetic counseling for patients and their affected family members.[52-56] Genetic testing has evolved to become an important strategy to complement clinical findings and to confirm a diagnosis.[53,57] Therefore, confirming a molecular diagnosis through genetic testing can help healthcare providers to assist patients to access the latest treatment options for precision medicine or qualify for clinical trial participation as an important part of care for patients with inherited retinal diseases in the evolving field of gene therapy.[55–59]

Causal Genes and Available Treatments: The Evolution of the Importance of Genetic Testing

Although not always preformed, the current consensus is that genetic testing is essential for patients with inherited retinal diseases.[60,61] Inherited retinal diseases are a group of clinically and genetically heterogeneous degenerative disorders.[62] Many potential targets are available for therapy for inherited retinal diseases, as over 270 disease-causing genes for monogenic inherited retinal diseases have been identified.[63] With the over 300 causal genes discovered thus far,[63] each gene has numerous variants associated with diseases that range from point mutations to large changes (e.g., deletions and duplications).[60] Given the increasing number of retinal gene therapy clinical trials and other gene or mechanism-driven interventions with promising results,[64] finding the disease-causing genetic etiologies of inherited retinal diseases has not only critically important diagnostic, counseling, and prognostic implications for affected patients but also important potential therapeutic implications.[60] As gene therapy opportunities for inherited retinal diseases continue to emerge and progress, and other gene-specific treatments are also being developed in addition to the approved gene therapy, additional therapeutic options for inherited retinal diseases are quickly becoming a reality.[64] Therefore, identifying the pathogenic genetic etiologies of inherited retinal diseases is no longer medically necessary only for diagnostic, counseling, and reproductive risk assessment purposes but also for compelling therapeutic implications and is a top priority in the field of inherited retinal diseases.[60] However, the best approach for genetic testing in patients with inherited retinal diseases is still not established with consensus.[60]

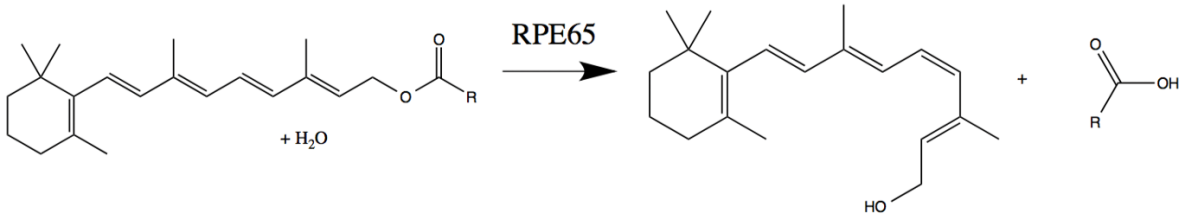
Identified Retinal Disease Genes[63]



RPE65 Gene Plays a Key Role in Vision

The *RPE65* gene, which is expressed in the retinal pigment epithelium, plays a key role in the retinoid cycle as it encodes retinoid isomerohydrolase.[19] This enzyme regenerates *11-cis* retinal, the chromophore that plays an essential role in phototransduction in photoreceptor cells.[20] Bi-allelic loss-of-function mutations in *RPE65* result in either a lack of *RPE65* protein or protein that is non-functional. Without this protein, photoreceptors have severely impaired responses to light and ultimately degenerate.[21] Retinal pigment epithelium-specific 65 kDa protein, or retinoid isomerohydrolase, is an enzyme of the vertebrate visual cycle that is encoded in humans by the *RPE65* gene. *RPE65* is expressed in the retinal pigment epithelium (RPE, a layer of epithelial cells that nourish the photoreceptor cells) and is responsible for the conversion of all-trans-retinyl esters to 11-cis-retinol during phototransduction.[19-22] 11-cis-retinol is then used in visual pigment regeneration in photoreceptor cells.[7-10] *RPE65* belongs to the carotenoid oxygenase family of enzymes.[19-22]

Reaction Completed by RPE65 in the Retinoid Cycle



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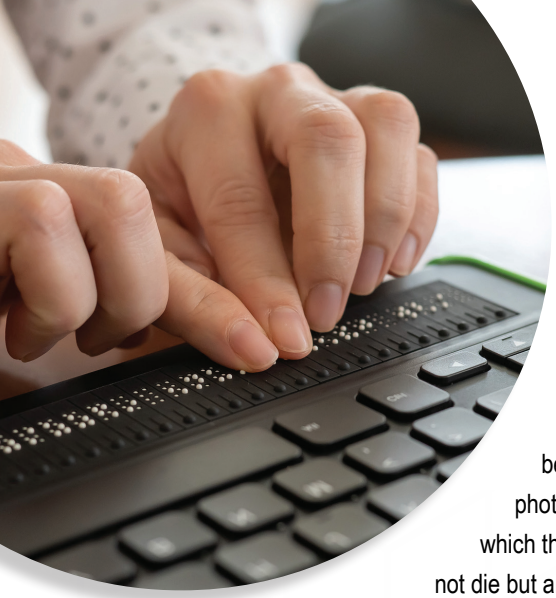


Inherited Retinal Diseases Are the Leading Cause of Blindness

Approximately 1 in 2,000 people worldwide are affected by inherited retinal diseases.[4,65-68] This group of disorders is a leading cause of blindness and are typically characterized by photoreceptor dysfunction, followed by retinal cell death and include rod-cone, cone-rod, isolated cone and macular dystrophies, and cone and rod dysfunction syndromes.[65,69–73] Inherited retinal disorders can be classified as panretinal pigmentary retinopathies with pigmentary clumping occuring secondary to photoreceptor death; macular dystrophies with only central retinal involvement; stationary conditions in which the photoreceptors do not die but are nonfunctional; optic nerve disease which is primarily due to involvement of ganglion cells; and other less frequent diseases.[74,75] Although there are multiple inherited retinal disorders identified, many others are yet to be discovered.[76] Some of the most common inherited retinal diseases include retinitis pigmentosa, chorioretinal dystrophy, Stargardt macular dystrophy, achromatopsia, age-related macular degeneration, and Leber's congenital amaurosis.[77] As the global population grows and ages, the number of people with vision loss will also increase.[78] Treatments for inherited retinal diseases remain as an unmet medical need, but the huge disease burden caused by inherited retinal diseases and the advancements in retinal genetics, imaging, and molecular biology, have led to improved diagnosis and the development of novel therapeutics as well as clinical trials of investigational treatments.[77–83]

> Approximately 1 in 2,000 people worldwide are affected by inherited retinal diseases, which are a leading cause of blindness.

Common Inherited Retinal Diseases

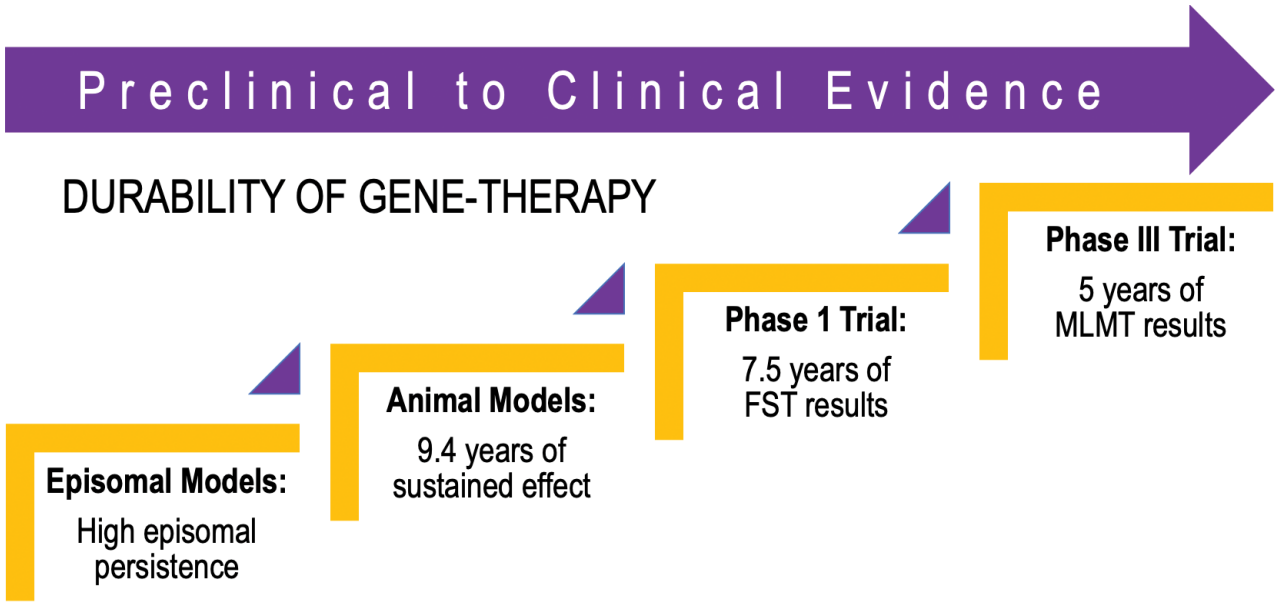
Achromatopsia	Patients legally blind from birth, usually having severely reduced visual acuity; photophobia; total color blindness; and nystagmus
Age-related macular degeneration	Leading cause of blindness for patients over 65 years of age in developed countries, with advanced stages being divided into the atrophic (dry) form and the exudative (wet) form
Choroideremia	Associated with chronic progressive vision loss, early onset night blindness, peripheral visual field reduction, with patients usually retaining good central visual acuity into their 50s
Leber's congenital amaurosis	Considered one of the most severe inherited retinal diseases, with patients having severe visual impairment starting in infancy
Retinitis pigmentosa	Most frequent inherited retinal diseases; X-linked retinitis pigmentosa, the most severe form of retinitis pigmentosa, has early onset in childhood and rapid progression to blindness by adulthood
Stargardt macular dystrophy	Associated with progressive central vision loss, and the leading cause of adolescent/young adult vision impairment

Durability of Therapeutic Effect for Gene Therapy

Although gene therapies have established clinical benefit, there is uncertainty related to duration of the single-intervention, one-time nature of gene-therapy treatment.[84] In a preclinical animal study, gene therapy demonstrated a sustained treatment effect of approximately 10 years.[85] Other animal studies demonstrated that gene therapy may have more pronounced effects when there is early diagnosis and intervention.[86] In addition, it has also been shown preclinically that later-stage treatment with gene therapy was also effective long-term.[87] In the case of gene-therapy for inherited retinal diseases, the clinical outcomes seen in humans are consistent with the findings from preclinical animal models.[84] Taken together, they support the long-term durability of treatment effect of voretigene neparvovec, with up to 7.5 years of sustained full-field light sensitivity threshold (FST) results from Phase I trials and 3, 4, and 5 years of sustained ambulatory navigation (multi-luminance mobility test [MLMT]), light sensitivity (FST), and visual field test outcomes from the Phase III trial.[88-90] Data such as these support the durability of *RPE65* gene-therapy with voretigene neparvovec.[88-90]

Data from clinical trials support the durability of *RPE65* gene-therapy with voretigene neparvovec.

Durability of Treatment Effect with *RPE65* gene therapies: Evidence from Preclinical to Clinical Studies of Voretigene Neparvovec[84]



FST=full-field light sensitivity threshold, MLMT=multi-luminance mobility test.

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