



Genetic Insights into Retinitis Pigmentosa: Current Perspectives and Future Therapeutic Strategies

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DESCRIPTION

Retinitis Pigmentosa (RP) represents a heterogeneous group of inherited retinal dystrophies that primarily affect the photoreceptor cells and Retinal Pigment Epithelium (RPE). It is characterized by progressive vision loss, night blindness, and peripheral visual field constriction, ultimately leading to central vision deterioration and legal blindness in many cases. With an estimated global prevalence of 1 in 4,000 individuals, RP poses a significant public health challenge and is a leading cause of inherited blindness. The past two decades have seen a dramatic shift in our understanding of RP from clinical diagnosis to the molecular and genetic mechanisms underpinning the disease, opening new possibilities for precision medicine and gene-based therapy.

Genetically, RP is one of the most diverse ocular disorders known, with over 80 genes implicated across various modes of inheritance, including autosomal dominant, autosomal recessive, and X-linked forms. Mutations in genes encoding structural proteins of photoreceptors, components of the phototransduction cascade, and elements involved in ciliary trafficking and intracellular transport all contribute to RP pathogenesis. Among the most frequently mutated genes are RHO (rhodopsin), USH2A, RPGR, EYS, and PRPF31. The variability in mutation type, gene expression, and affected pathways underlies the phenotypic diversity seen among RP patients, even within the same family.

Advancements in Next-Generation Sequencing (NGS) technologies, particularly whole exome and whole genome sequencing, have revolutionized the diagnosis of RP. These techniques enable the identification of disease-causing mutations with increasing sensitivity and cost-efficiency, allowing for molecular diagnosis in over 70% of RP cases. Genetic testing not only aids in confirming the clinical diagnosis but also facilitates carrier screening, genetic counseling, and eligibility assessment for gene-specific therapies and clinical trials.

Clinically, RP typically begins with rod photoreceptor degeneration, manifesting as nyctalopia and progressive peripheral field loss. As the disease advances, cone photoreceptors also degenerate, leading to central vision impairment and decreased visual acuity. Fundoscopic findings include bone spicule-like pigmentation in the mid-periphery, attenuation of retinal vessels, and optic

disc pallor. Retinal layers and loss of the ellipsoid zone, while fundus autofluorescence imaging may show a characteristic hyperautofluorescent ring surrounding the macula.

Despite the absence of a definitive cure, recent therapeutic developments offer hope for modifying the course of RP. One of the most significant breakthroughs was the FDA approval of voretigene neparvovec (Luxturna), a gene therapy for RPE65-mediated Leber congenital amaurosis and early-onset RP. This Adeno-Associated Virus (AAV)-based therapy delivers a functional copy of the defective gene to retinal cells, leading to sustained visual improvement in affected individuals. The success of Luxturna has catalyzed a surge of clinical trials targeting other RP-associated genes using AAV, lentiviral, and non-viral vectors.

Beyond gene replacement, other therapeutic strategies under investigation include gene editing, RNA-based therapies, and optogenetics. CRISPR/Cas9-mediated gene editing holds promise. Antisense Oligonucleotides (ASOs) are being tested for their ability to modulate splicing or suppress mutant transcripts, as in the case of USH2A and QRX421. Optogenetic therapies aim to restore light sensitivity to inner retinal neurons by introducing photosensitive proteins, potentially offering a therapeutic option for late-stage RP regardless of the causative mutation.

Retinal implants and prostheses represent an additional avenue for restoring vision in advanced RP. Devices such as the Argus II Retinal Prosthesis System convert visual information into electrical impulses that stimulate surviving retinal ganglion cells. While functional outcomes are limited, these technologies provide a proof-of-concept for vision restoration in end-stage retinal degeneration. Coupled with advancements in brain-computer interfaces and artificial intelligence, retinal prosthetics may evolve into more effective tools in the future.

Pharmacological approaches, including neuroprotective agents and antioxidants, have also been explored, though with variable success. Compounds such as Ciliary Neurotrophic Factor (CNTF), valproic acid, and vitamin A palmitate have been studied for their potential to slow photoreceptor degeneration. However, inconsistent results and safety concerns have limited their clinical adoption. Ongoing research seeks to identify novel drug targets and combinations that can support retinal cell survival and function.

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