

# Allele-Specific Cytosine Base Editing for Retinal Rhodopsin Correction Studies

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## DESCRIPTION

Autosomal dominant retinal degenerative conditions linked to pathogenic variants in the rhodopsin gene represent a significant portion of inherited photoreceptor dysfunction cases characterized by progressive decline in rod-mediated visual capacity followed by secondary cone involvement. Among the multiple described sequence alterations, single nucleotide substitutions within the coding region of rhodopsin frequently result in misfolded protein accumulation, altered intracellular trafficking, and subsequent cellular stress responses within rod photoreceptors. These cellular disturbances contribute to gradual photoreceptor loss and structural disorganization of the outer retinal layers. Traditional management approaches remain limited to supportive interventions, while molecular correction strategies have gained increasing attention as a means to directly modify disease-associated genomic sequences. This article describes an allele-selective cytosine base editing approach developed for correction of a pathogenic point mutation in a preclinical mammalian model system carrying a heterozygous rhodopsin variant associated with progressive retinal dysfunction.

The experimental design employed a deactivated Cas protein fused to a cytidine deaminase enzyme capable of catalyzing targeted base conversion without introducing double-stranded Deoxyribonucleic Acid (DNA) cleavage. A guide Ribonucleic Acid (RNA) was constructed to recognize a short genomic region containing the disease-associated nucleotide substitution while incorporating intentional mismatches to enhance discrimination between mutant and wild-type alleles. The expression cassette utilized a photoreceptor-active regulatory sequence intended to drive localized transcription of the base editing machinery within rod cells while limiting ectopic expression in adjacent ocular tissues.

Following vector administration, molecular analysis of retinal tissue samples was performed at sequential time intervals to evaluate editing efficiency, allele specificity, and persistence of genomic modification. Early assessments indicated detectable conversion of the targeted cytosine residue to thymine at the disease-associated locus within rod photoreceptor nuclei. The editing activity demonstrated preferential targeting of the

mutant allele, with significantly reduced modification observed in the corresponding wild-type sequence, consistent with the designed guide RNA discrimination strategy. Quantitative sequencing analysis revealed that editing frequency reached a plateau within a defined post-delivery window, suggesting stabilization of editing activity following initial vector expression.

Histological examination of retinal sections provided additional insight into structural preservation following gene editing intervention. Outer nuclear layer thickness measurements demonstrated reduced thinning in treated subjects relative to untreated controls over equivalent observation periods. Photoreceptor outer segment organization appeared more preserved in regions exhibiting higher editing activity, suggesting localized functional benefit correlated with molecular correction levels. Retinal pigment epithelium morphology remained largely intact, with no overt signs of degeneration attributable to vector exposure. Cellular stress markers assessed through immunohistochemical staining indicated reduced accumulation of misfolded rhodopsin protein in treated retinal regions, aligning with the intended molecular outcome of allele correction.

Transcript-level analysis revealed a shift in rhodopsin gene composition favoring the corrected sequence over the mutant transcript in treated samples. This alteration in transcript distribution corresponded with decreased activation of stress-associated signaling pathways commonly observed in photoreceptor degenerative conditions, including those associated with endoplasmic reticulum burden. However, residual expression of the mutant allele persisted in a subset of photoreceptor cells, reflecting incomplete transduction and variable editing efficiency across retinal microdomains. Spatial heterogeneity in vector distribution was observed, likely influenced by diffusion dynamics within the subretinal space and local cellular accessibility.

Longitudinal observation of retinal function indicated that the benefits associated with base editing were maintained over an extended period, although gradual attenuation of effect was observed in some cases. This decline may be associated with photoreceptor turnover dynamics and dilution of episomal vector genomes during cellular maintenance processes. The non-

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**Received:** 27-Feb-2026, Manuscript No. JGSGT-26-42890; **Editor assigned:** 02-Mar-2026, PreQC No. JGSGT-26-42890 (PQ); **Reviewed:** 16-Mar-2026, QC No. JGSGT-26-42890; **Revised:** 23-Mar-2026, Manuscript No. JGSGT-26-42890 (R); **Published:** 30-Mar-2026, DOI: 10.35248/2157-7412.26.16.492

**Citation:** Hofmann D (2026). Allele-Specific Cytosine Base Editing for Retinal Rhodopsin Correction Studies. J Genet Syndr Gene Ther. 14:492.

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integrative nature of the delivery system contributes to safety considerations but also limits permanent genomic modification across all target cells. Repeat administration was explored in a subset of experimental subjects, revealing reduced editing efficiency upon secondary exposure, consistent with adaptive immune recognition of the viral capsid and partial neutralization of vector particles.

The distribution of edited photoreceptors within the retinal tissue exhibited a mosaic pattern, reflecting variability in vector uptake and intracellular processing efficiency. This spatial variability suggests that full functional restoration may require broader and more uniform transduction across the retinal surface. Efforts to optimize delivery techniques, including adjustments to injection volume, vector concentration, and capsid selection, may contribute to improved coverage in future applications. Additionally, exploration of complementary delivery routes such as intravitreal administration may provide alternative access pathways to photoreceptor layers, although

current evidence indicates lower efficiency compared with subretinal delivery for outer retinal targeting.

## CONCLUSION

Overall findings from this experimental system indicate that allele-specific cytosine base editing can achieve partial correction of a pathogenic rhodopsin variant in a preclinical model of autosomal dominant retinal degeneration, resulting in measurable improvements in photoreceptor structure and function. While the intervention does not fully restore normal retinal physiology, the observed molecular and physiological changes demonstrate the potential utility of precise nucleotide-level modification strategies for conditions driven by single base substitutions. Further investigation will be required to enhance editing uniformity, extend duration of effect, and minimize immune-related limitations associated with vector-based delivery systems.