Exploring Genetic Therapeutic Strategies to Combat Vision Loss in Usher Syndrome Type 1C

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Introduction

- Usher Syndrome is an autosomal recessive genetic disorder that is the most common cause of hereditary deaf-blindness in the world.[1]
- There are 4 clinical types of Usher Syndrome (USH1-4) that differ in severity and symptoms.[1,2]
- USH1 is the most severe and is characterized by congenital sensorineural hearing loss, vestibular areflexia, and adolescent onset of retinitis pigmentosa.[3]
- The USH1C c.216G>A mutation (216A) accounts for nearly all the USH1 cases in the Acadian populations of Louisiana.[4] The (216A) mutation is responsible for aberrant RNA splicing that encodes a truncated harmonin protein, which is a structural protein found in cochlear hair cells and photoreceptors.[5,6]
- Gene replacement therapy with AAV vector and antisense oligonucleotides (ASOs) designed to target the 216A mutation in mouse model with USH1C have been demonstrated to correct splicing and recover hearing loss, balance, and vision. [6-11]
- In this study, we aim to optimize gene replacement delivery and antisense oligonucleotide chemistry to improve upon these results.

USH1C Splicing & ASO

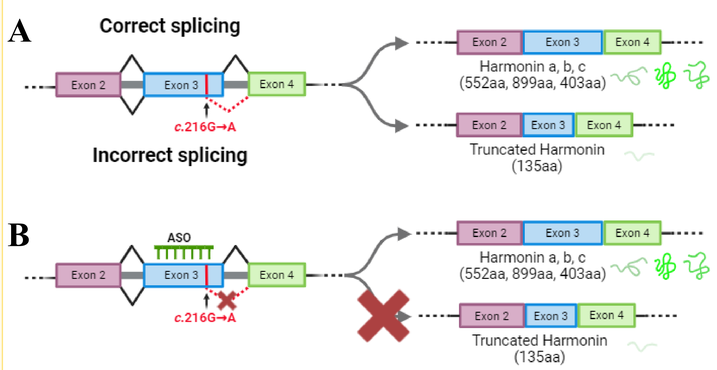

Fig 1. Using ASO to correct aberrant splicing in USH1C. (A) Normal splicing of USH1C can result in three different functional harmonin isoforms (a,b,c). The 216A mutation in exon 3 leads to aberrant splicing and a truncated harmonin protein. (**B**) ASO treatment targets the 216A mutation to prevent abnormal splicing.

Methods

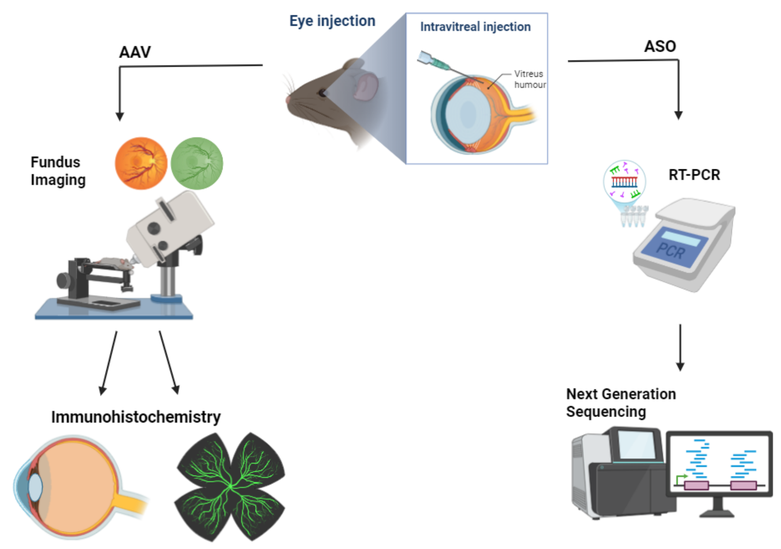

Fig 2. Methodology for evaluating AAV transduction and ASO-mediated splicing correction. Wild-type and USH1C216AA mice received a single dose of either a reporter AAV (AAV44.9-(E531D)-CBA-GFP) vector or antisense oligonucleotides with a 2'OMe backbone chemistry.

Fundus Imaging

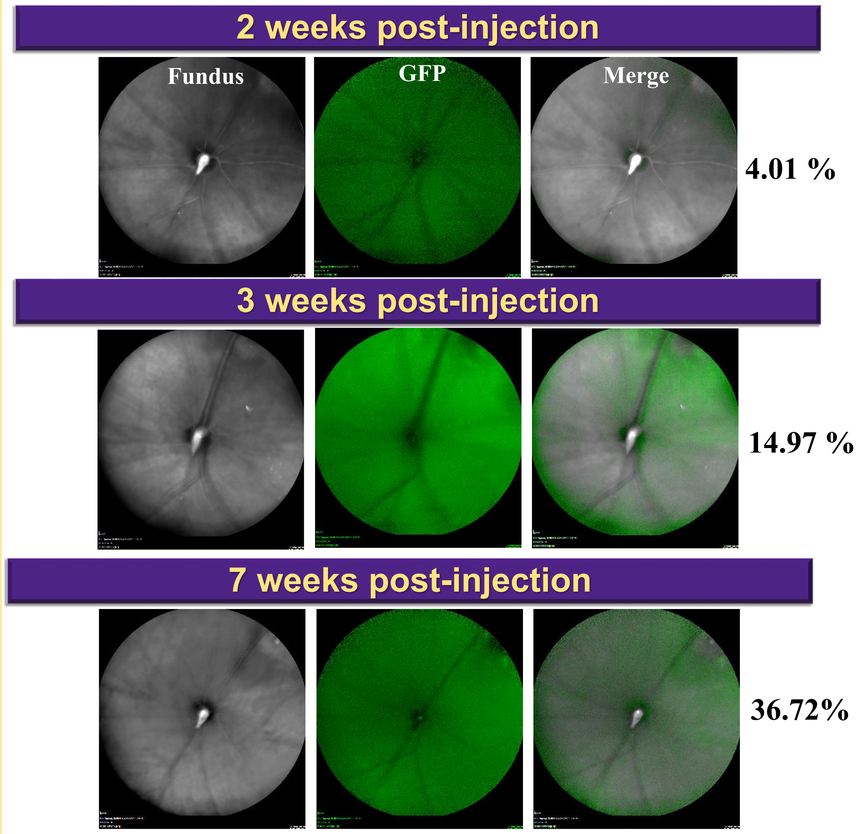

Fig 3. Fundus imaging of GFP expression following AAV injection. The columns from left to right display the plain fundus, the GFP fluorescence, and the composite of both images. GFP area of the composite was calculated.

Retinal GFP Expression

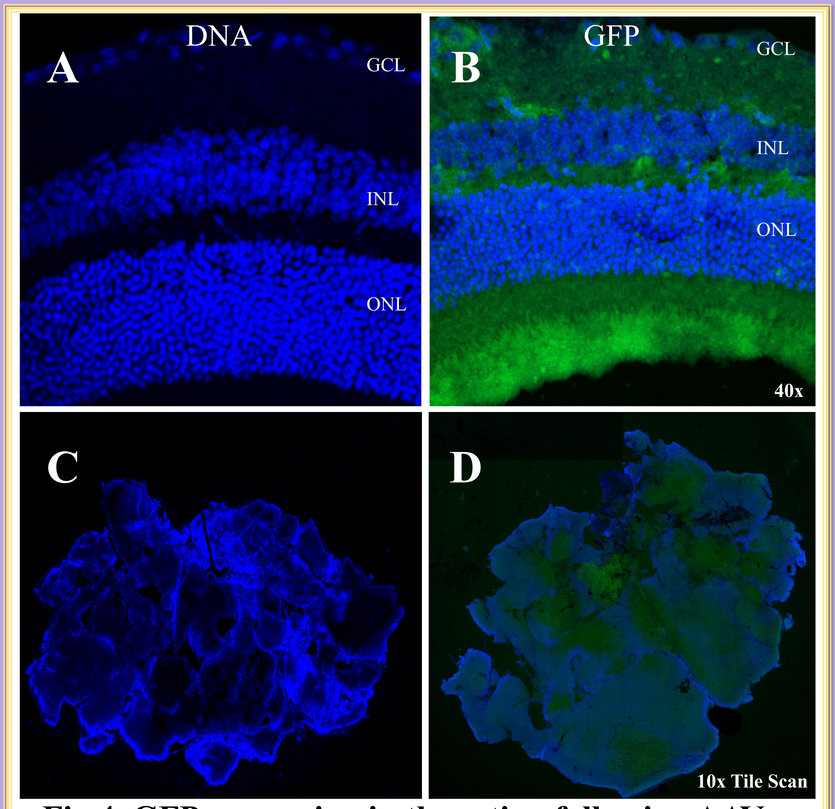

Fig 4. GFP expression in the retina following AAV IVI. (A) Retinal cross section of un-injected eye. (**B**) Injected eye. (**C**) Retinal whole mount of un-injected eye. (**D**) Injected eye. Green fluorescence indicates GFP. GCL = Ganglion cell layer; INL = inner nuclear layer; ONL = outer nuclear layer.

Results & Conclusion

- AAV mediated GFP expression is visible on fundus imaging and immunohistochemistry after IVI.
- Sequencing of analyses of ASO treated mice is pending.
- AAV44.9 vector can transduce cells in mouse retina via IVI. Future studies will compare the therapeutic effects of AAV-Ush1c versus ASO treatment on visual function in USH1C mice.

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Images in Fig. 1 & 2 were created using Biorender.

Acknowledgements

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