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"Development of genetic strategies to treat vision loss in Usher syndrome Type 1C (USH1C)"

Background: Usher Syndrome (Usher) is the most common genetic cause of deaf-blindness, characterized by the loss of hearing, vestibular function, and vision. Three clinical types (USH1-3) and 10 genes are associated with the disease. USH1 is the most severe with congenital severe-profound sensorineural hearing loss and vestibular areflexia, and childhood onset of retinitis pigmentosa. Mutations in the *USH1C* gene account for 6-15% USH1, however *USH1C c.*216G>A (216A) accounts for nearly all USH1 cases in the Acadian populations in U.S. and Canada. The 216A splicing mutation results in a truncated harmonin protein, and photoreceptor and cochlear hair cell dysfunction. While the genetics of Usher is well studied, treatment options remain limited. Additionally, the clinical natural history of the visual loss – when symptoms begin and how quickly they progress – is not known. The objectives of this study are to develop genetic strategies to target the 216A mutation using adeno-associated viruses (AAV) to deliver gene-editing tools in USH1C mice, and to fill the knowledge gaps in the natural history of visual loss in USH1C patients.

Methods: To evaluate the safety and efficiency of targeting retinal cells with gene therapy vectors, wild-type (WT) mice were treated with AAV vectors expressing a green fluorescent protein (GFP) via subretinal injection. Retinas were harvested at 2- and 4-weeks post-injection and examined for AAV-mediated GFP expression using immunohistochemistry. To determine the progression of visual loss in USH1C, patients with genetic confirmation of USH1C disease aged 12 – 70 years are being recruited to participate in a prospective natural history study across three clinical centers using standard and novel visual parameters measured at 4 clinic visits in 6-month intervals.

Results: Preliminary assessment of treated mouse retinas show AAV-mediated GFP expression across all layers of the retina, including the photoreceptor inner/outer segment and nuclear layers in 20-25% of the retina near the site of injection. 8 USH1C participants (1 pediatric, 6 young adult, 1 adult) have been enrolled in the prospective natural history study and completed their first clinic visit. Two participants have also completed their second visit. Preliminary data suggest visual acuity declines as photoreceptors degenerate with age.

Conclusion: Our preclinical results show that AAVs can target photoreceptors when delivered locally via subretinal injection. A careful understanding of the natural progression of the visual loss in USH1C will provide outcome measures to guide a future clinical trial and improve care for patients.