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"Motor function, coordination, and balance are significantly improved in Usher syndrome Type 1C mice treated with antisense oligonucleotides"

Background: Usher syndrome (Usher) is an autosomal recessive genetic disease that is characterized by concurrent hearing and vision loss. Some patients also have imbalance. Usher has 3 clinical presentations, USH1-3, each differing in the severity and onset of symptoms. A 216G>A mutation (216A) in the *USH1C* gene accounts for nearly all the USH1 cases in the Acadian populations of Louisiana and Canada. The 216A splicing mutation leads to a dysfunctional harmonin protein that is required for the proper development and function of retinal photoreceptors and inner ear hair cells. We created a mouse model of USH1C by knocking in the 216A mutation and these mice also have concurrent hearing, balance, and vision loss similar to patients. Next, we developed an antisense oligonucleotide (ASO) treatment that targets the 216A mutation. Treatment of USH1C mice with ASO shows short-term rescue of hearing, balance, and vision. The aim of this study was to determine the effect of ASO therapy on motor function, coordination, and balance behavior in USH1C mice.

Methods: USH1C mice were treated locally to the inner ear via utricle injection at postnatal day 2 with ASOs targeting the 216A mutation. Motor function, coordination, and balance behavior were assessed by rotarod testing in USH1C-ASO, USH1C-control (untreated), and wild type littermates at 12 months of age. Briefly, the mice are placed in individual lanes on the Rotarod apparatus at a baseline rotation of 4 RPM that accelerates to 40 RPM over 240 seconds. Three trials per mouse separated by a 10-minute rest period were recorded and the average latency to fall was calculated. Mice had been previously acclimated to the rotarod using the same testing paradigm 2-3 days prior to the experimental run.

Results: Latency to fall was significantly longer in USH1C mice treated with ASOs compared to untreated USH1C controls (92 seconds and 4 seconds, respectively). Additionally, the latency to fall for the USH1C mice treated with ASOs was significantly greater than wild type littermate control mice (92 seconds and 64 seconds, respectively).

Conclusion: These preliminary data suggest that antisense therapy significantly improves musculoskeletal coordination and balance in USH1C mice. These data also support the efficacy of ASO treatment in restoring balance behavior in Usher syndrome.