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"Natural History of Visual Loss in USH1C"

Purpose: Usher syndrome (USH) is a rare genetic disorder characterized by the multi-sensory loss of hearing, balance, and vision; however, the natural clinical course—when these losses begin and how quickly they progress—is not known. Four clinical types (USH1-4) and 10 genes (subtypes) are associated with the disease based on the severity and age of onset of the symptoms. Approximately 10% of USH1, the most severe form, is caused by mutations in the *USH1C* gene; however, nearly all cases are caused by the *USH1C* c.216G>A founder mutation among the Acadian populations in Canada and Louisiana. We are conducting a multicenter, prospective natural history study (NHS) of visual loss in USH1C at all stages of disease to improve our understanding of the natural progression and identify potential clinical trial participants and robust outcome measures that can be used to guide future clinical trials.

Methods: Demographic, ophthalmic history, and genetic information was obtained, and longitudinal patient-reported and clinical vision data are being collected from adolescent, young adult, and adult USH1C patients over 4 clinical visits: at baseline, 6-, 12-, and 18-months.

Results: Currently, 21 consenting participants (adolescent (n=6), young adult (n=11, 1 excluded due to nystagmus), adult (n=4)) with genetic confirmation of USH1C disease are enrolled. 43% are female, and 81% (n=17/21) have at least one copy of the *USH1C* c.216G>A mutation. Average (ETDRS) Visual Acuity and Low Luminance Visual Acuity at baseline were 0.15 and 0.28 (adolescents), 0.23 and 0.36 (young adults), and 3.26 and 3.45 (adults) LogMAR, respectively. Intraocular pressure was within normal limits for all visits across all patients. Reading speed, contrast sensitivity, color vision, microperimetry thresholds, and kinetic visual field isopter area declined over time. Analysis of the blue-red full-field stimulus sensitivity threshold difference suggests that retinal light sensitivity thresholds transitioned from rod-mediated to cone-mediated as the age of participants increased. The perifoveal ring of hyperautofluorescence progressively became more constricted as the age of participants increased. Additional analyses of retinal structure and sensitivity using optical coherence tomography are ongoing.

Conclusion: Natural history and outcome measures data for USH1C patients are important to guide clinical trials and improve our understanding of the natural disease progression.