Researchers at UH Ear, Nose & Throat Institute and Case Western Reserve University School of Medicine have developed not one, but two mouse models engineered to carry the most common mutation in Usher syndrome III causative gene (Clarin-1) in North America.

ANIMAL MODELS DEVELOPED FOR STUDY OF USHER SYNDROME

Models Engineered to Carry Mutation and Mimic Disease Onset in Humans

Usher syndrome is an incurable genetic disease that is the most common cause of the dual sensory deficits of deafness and blindness. Clinically, it is subdivided into types I – III and all patients ultimately arrive at the same consequence, the progressive loss of hearing and vision. The focus of this study is Usher type III. More than a dozen genetic mutations are associated with Usher III, with N48K mutation in Clarin-1 being the most prevalent.

As reported in the Journal of Neuroscience in July 2012, **Kumar Alagramam, PhD**, *Anthony J. Maniglia Chair for Research and Education, Director of Research and Associate Professor of Otolaryngology, Case Western Reserve University School of Medicine* and his co-investigator **Yoshikazu Imanishi, PhD**, *Assistant Professor, Case Western Reserve University Department of Pharmacology,* developed the first mouse model to mimic the N48K mutation in Usher III patients. This model allowed researchers to understand the pathophysiology in fine detail, as there is no noninvasive way to evaluate soft tissue pathology in the human inner ear.

The genetically engineered mouse developed hearing loss similar to clinical presentations observed in Usher III patients with N48K mutation. However, unlike real world onset, which is gradual, the genetically engineered mouse developed hearing loss very quickly, and injecting the potential therapeutic agents early is toxic to the young animal. This necessitated an even more recent and significant progression, which is the development of a newer mouse model in which the onset of hearing loss is delayed. By more closely mimicking the disease's onset in humans and allowing testing on more mature animal models, this model provides a better platform to administer the calculated therapeutic doses and even adjust them if needed.

The immediate goal is to develop a drug therapy to prevent hearing loss in the mice, but the other potential that this newer animal model presents is the possible development of gene replacement therapy. Tests are under way to determine if the hearing loss in the newer mouse model can be predicted in terms of delayed onset, and preliminary data indicates this to be the case.

At the end of 2013, testing on the new mouse concluded and longitudinal testing began, with drug therapies administered every other day. The study is projected to last through June 2014. Funding was, and continues to be, provided by the Usher III Initiative and the National Institutes of Health through Case Western Reserve University School of Medicine.