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Preclinical development shows promise to treat hearing loss with Usher syndrome III

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A new study published in the July 11 issue of the *Journal of Neuroscience* details the development of the first mouse model engineered to carry the most common mutation in Usher syndrome III causative gene (Clarin-1) in North America. Further, the research team from Case Western Reserve University School of Medicine used this new model to understand why mutation in Clarin-1 leads to hearing loss.

Usher Syndrome is an incurable genetic disease and it is the most common cause of the dual sensory deficits of deafness and blindness. It affects an estimated 50,000 Americans and many more worldwide. Clinically it is subdivided into types I-III based on the degree of deafness and the presence of balance disorder and each type is associated with distinct genes. While the progression of the disease is different with each type, all patients ultimately arrive at the same consequence. 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 mutation in Usher III patients in North America. Since N48K mutation originated in Europe, results of this study will be of significance to a subset of Usher III patients in Europe as well.

"With the prospective of designing and exploring therapies for Usher III patients with N48K mutation, this is a significant preclinical finding," says Kumar Alagramam, PhD, associate professor of otolaryngology head & neck surgery, genetics, and neurosciences and senior author of the manuscript. "This key understanding of how deafness occurs in Usher III is based on three years of collaborative work."

This new study reports on the first mouse model that mimicked the N48K mutation in Usher III patients. The genetically engineered mouse developed hearing loss similar to clinical presentations observed in Usher III patients with N48K mutation. This model allowed researchers to understand the pathophysiology in fine detail, as there is no non-invasive way to evaluate soft tissue pathology in the human inner ear.

The new study explains why the mutation in the N48K mutation in Clarin-1 leads to hearing loss – mislocalization of mutant protein in mechanosensory hair cells of the inner ear. Using this new Usher III model, researchers can now explore prospective therapeutics to rescue mutant protein localization and hearing. If successful, this approach could serve as a model to treat Usher I and II associated with missense mutation.

In 2009, Alagramam et al reported on the first mouse model of Usher III. The first mouse model was gene knockout mutation and most recent mouse model is a missense mutation, the first model of its kind for Usher III.

Provided by Case Western Reserve University