Gene Therapy Treats Genetic Hearing Loss in Aged Mouse Model

Groundbreaking findings published in Molecular Therapy set the stage for human trials.

The prevalence of TMPRSS3 mutations makes it an excellent potential target for gene therapy.

Researchers successfully used gene therapy to help restore hearing in a mouse model mimicking genetic hearing loss in humans, according to a study by University of Miami Miller School of Medicine and Harvard Medical School researchers published in Molecular Therapy.

The next step is to study the therapy in humans with common type of genetic hearing loss, said Xue Zhong Liu, M.D., Ph.D., one of the corresponding authors and the Marian and Walter Hotchkiss Endowed Chair in Otolaryngology at the Miller School.

“Hearing loss affects 15 to 26% of the world’s population. The gene TMPRSS3 is necessary for normal hearing, and mutations in TMPRSS3 account for about 9% of genetic hearing loss,” Dr. Liu said. “TMPRSS3 mutations affect function and survival of inner ear and hearing nerve cells, which have been associated with age-related hearing loss.”
Hearing loss associated with mutations in TMPRSS3 can range from mild to profound and is generally progressive. The prevalence of TMPRSS3 mutations and impact of this mutation on people’s lives make it an excellent potential target for gene therapy. The resulting gene therapy could help patients with and without cochlear implants, which today are the only treatment option for this type of hearing loss, according to Dr. Liu.

“Patients with these mutations have significant amounts of residual hearing. This would make it an attractive target for potential rescue therapy,” he said. “And prevention of further hearing degeneration in patients undergoing hearing preservation cochlear implantation would lead to better hearing outcomes.”

Focusing on TMPRSS3 Gene Mutations

Dr. Liu and the Miller School team recommended focusing the study on the most common form of TMPRSS3 mutations, called DFNB8, which has been reported across populations. Miller School researchers also generated the mouse model used in this study, which mimicked post-lingual hearing loss in TMPRSS3 patients.

“In humans with this mutation, hearing loss does not manifest until adulthood. Much like humans, mice with the mutation develop delayed hearing loss, which made the model valuable for the study,” Dr. Liu said.

Another corresponding author Zheng Yi Chen, D.Phil., an investigator in the Eaton-Peabody Laboratories at Mass Eye and Ear, said the findings suggest that a virally mediated gene therapy, either by itself or in combination with a cochlear
implant, could potentially treat genetic hearing loss.

The authors found that a single injection of gene therapy targeted to the mutation resulted in sustained recovery of auditory function in the mouse model.

“This was also the first study that has rescued hearing in aging mice, which points to the feasibility of treating DFNB8 patients with DFNB8 even at an advanced age. The study also establishes the feasibility of other gene therapies in the aged population,” Dr. Chen said.

The Miller School and Harvard are collaborating on treatment experiments for genetic hearing loss and have started to conduct an international multicenter study on this form of hearing loss to prepare for human gene therapy trials, said Dr. Liu.