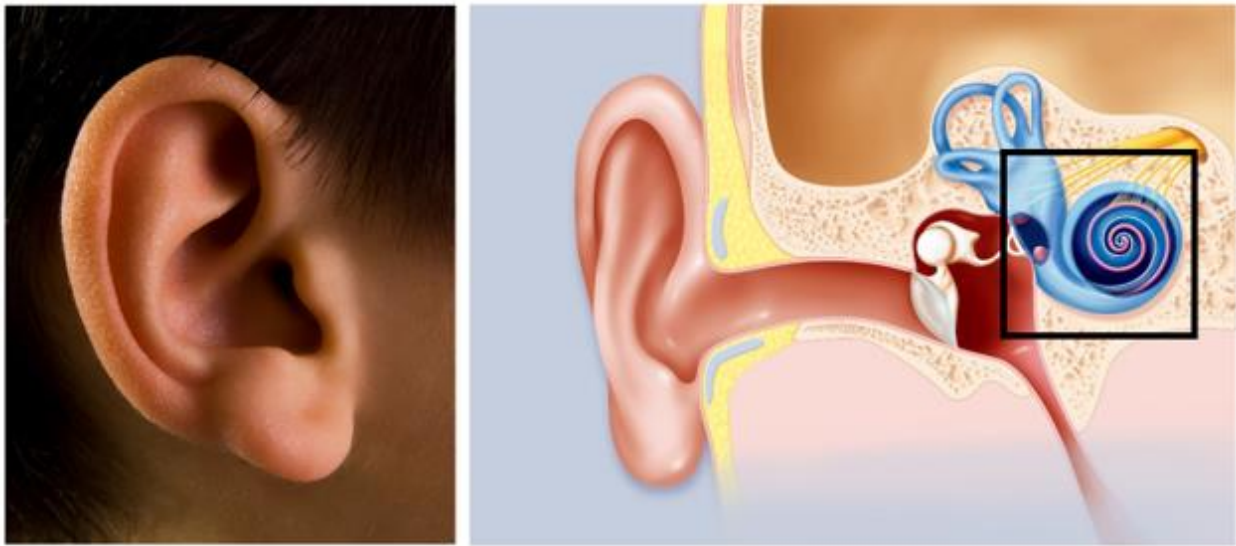




Promising results from **gene therapy to treat a form of childhood deafness** will be reported at the annual meeting of the [Association for Research in Otolaryngology](#) on February 3rd.

More than 1.5 billion people worldwide are affected by hearing loss. Of those, 26 million were born deaf. The majority (~60%) of hearing loss in infants and children is due to genetic causes. The recent gene therapy trials have focused on replacing a defective gene in the cochlea of the inner ear with a functional gene for **otoferlin**—a protein that functions in synapses and allows inner ear sensory **hair cells** to transmit sound from the ear to the brain.



How do we hear? Human hearing occurs when sound travels down the ear canal, vibrating a thin tympanic membrane. The membrane transmits the vibrations to the middle ear where three tiny bones (malleus, incus, stapes) carry the vibrations to the cochlea (outlined with a black box in the diagram) of the inner ear. The vibrations cause fluid within the cochlea to move, swishing the fluid over the hair cells along the cochlear walls. Movement of the hair cells gets translated into signals that travel along nerves from the inner ear to the brain, which then interprets the signals as sound. Otoferlin is necessary for the hair cells to work properly, so children born with defective otoferlin are deaf.

Otoferlin mutations are a relatively rare cause of genetic congenital deafness, accounting for approximately 1 - 8% of cases. However, researchers identified this form of deafness as a good candidate for initial gene therapy trials because of its connection to a single causative gene, the gene's activity being limited to one type of inner ear cells, and the way that hair cells survive for several years in patients with defective otoferlin despite their hearing loss.

For the gene therapy trials, a small volume of liquid containing the normal otoferlin gene (carried by an adeno-associated vector) is carefully injected into the cochlea, where the gene is expressed in the hair cells with its protein product incorporated into the synapses to restore the function. Around the world in the U.S., China, and Europe, five such trials are either underway or about to start. Children in the reported trials have been followed for 6 months to a year after treatment so far, without any significant safety concerns or complications.

The first trial, supported by the National Natural Science Foundation of China and Shanghai Refresh Gene Therapeutics, has been led by Dr. Yilai Shu of Shanghai Fudan Eye & ENT Hospital China, and Dr. Zheng-Yi Chen, who is at the Eaton-Pebody Laboratory of the Mass Eye and Ear and an Associate Professor of Otolaryngology at Harvard Medical School in Boston, MA. Of the six children with profound deafness in the trial, five gained partial hearing and speech capability after otoferlin gene therapy. The study was first reported at the European Society of Gene and Cell Therapy Conference in Brussels, Belgium, in October 2023. The study was published in *The Lancet* in January 2024.

Another trial—a collaboration between Regeneron and Decibel Therapeutics (which was acquired by Regeneron in 2023)—will be presenting 12-week results from the first child (10 months old at treatment) in their study (CHORD Trial investigating DB-OTO). In October 2023, preliminary results at 6 weeks showed improvement in hearing on audiometry testing and auditory brainstem response. Professor Manohar Bance, M.B., who is leading the Cambridge University Hospital trial site in the United Kingdom, said “We look forward to following this young child and others further to determine if DB-OTO gene therapy can provide clinically meaningful and durable hearing as they are learning to interact with the world.” The trial is ongoing and enrolling at clinical sites in the U.S., United Kingdom and Spain.

The first child to receive otoferlin gene therapy in the U.S. was Aissam Dam, an 11-year-old boy from Morocco who had been completely deaf since birth. He was enrolled in a trial at the Children's Hospital of Philadelphia, supported by a small biotechnology firm called Akouos which is owned by the pharmaceutical company Eli Lilly. His father reports that within days of starting the trial, Aissam had begun to hear traffic noises. Hearing tests two months after the trial found near-normal hearing in his treated ear.

Researchers from all five of the trials will present their findings at the Presidential Symposium of the [Association for Research in Otolaryngology](#) conference, which will be held in Anaheim, CA, the first week in February.