Canadian Audiologist
The Official Publication of the Canadian Academy of Audiology

Gene Therapy for Children with Deafness: We Are Almost There, At Least for Single Gene Mutations

Published May 7th, 2024

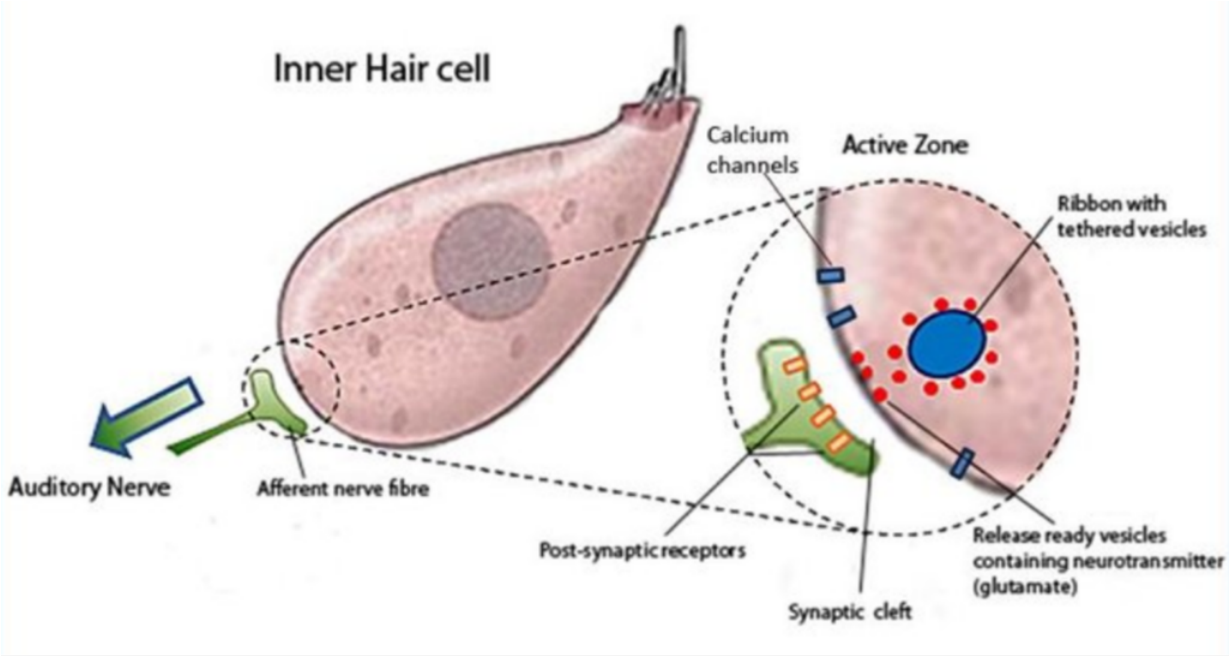
Robert V. Harrison, PhD, DSc

This year (2024), at various international audiology and otolaryngology conferences (e.g., AAA; ARO), we have heard about preliminary findings on the restoration of hearing in children after gene therapy. This follows from at least a decade of research studies in animal models of deafness due to single gene mutations where the correct gene insertion has been shown to be (a) possible, (b) safe, and (c) with some limited degree of efficacy. There are numerous up-to-date reviews of such studies.[1–4]

In brief, a few salient facts. The gene therapy research has largely been focused on hearing loss related to single gene mutations, because in these cases the genetic material to be inserted is unambiguous. Various modes of delivery of genetic material into the cochlea, including safety factors, have been explored. The current method of choice is to contain the genetic material within a virus carrier (adeno-associated virus) and introduce it into the inner ear via the round window.

One of the most often explored genes is the otoferlin gene (OTOF). When absent (as in knock-out mice) or mutated, there is dysfunction of the inner hair-cell synapse, and this is clinically manifest as auditory neuropathy (ANSD). In experimental models, (mostly in mice) the gene therapy results can be assessed in objective measures of hearing function, for example in ABR or OAE recordings,

as well as detailed anatomical studies of hair-cell integrity. In human studies, similar objective measures can be used, and indeed are essential in very young infants before behavioural testing can be achieved. Needless to say anatomical studies are not possible in children (although in the future, high-resolution neuro-imaging methods may become available). Given the extensive research background on hair-cell synaptopathy caused by OTOF gene mutations, it is not surprising that the initial human gene therapy clinical testing has been in children with otoferlin caused ANSD.



The recent major news has come from a study jointly led by investigators from the Massachusetts General Brigham Hospital (Mass Eye and Ear) and the Eye & ENT Hospital of Fudan University in Shanghai, China. As validated in previous animal research, the clinical study used an adeno-associated virus (AAV) holding the human *OTOF* gene, surgically introduced into the inner ear. In this gene therapy trial, six children with otoferlin related hearing loss (autosomal recessive deafness 9) were tested. Initially all six children had total deafness as indicated by ABR threshold measurements (elevations >95dB). After 26 weeks, five children showed a hearing recovery (40-57 ABR threshold improvement) as well as better speech perception. The full results of the study have recently been published in the *Lancet*.[5]

This important clinical trial has demonstrated the effectiveness of gene therapy in restoring hearing function for children suffering from hereditary deafness. In addition, the work contributes to an understanding of the safety of AAV vector used for gene insertion into the human inner ear. Thus far, the clinical study described here is the first to “hit the headlines,” but I suspect many more are planned or in the pipeline. There is more to come.

References

1. Moser T, Chen H, Kusch K, Behr R and Vona B. Gene therapy for deafness: are we there now? EMBO Mol Med. 2024;16:675-677. https://doi.org/10.1038/s44321-024-00058-6

2. Rankovic V, Vogl C, Dörje NM, Bahader I, Duque-Afonso CJ, Thirumalai A, Weber T, Kusch

K, Strenzke N and Moser T. Overloaded Adeno-Associated Virus as a Novel Gene Therapeutic Tool for Otoferlin-Related Deafness. Front. Mol. Neurosci 2001;13:600051. doi: 10.3389/fnmol.2020.60005

3. Saidia AR, Ruel J, Bahloul A, et al. Current Advances in Gene Therapies of Genetic Auditory Neuropathy Spectrum Disorder. J Clin Med 2023;12:738. https://doi.org/10.3390/jcm12030738
4. Jieyu Qi, Liyan Zhang, Renjie Chai. AAV-based gene replacement: The promise of gene therapy for deafness. Molecular Therapy 2024;25:102181. https://doi.org/10.1016/j.omtn.2024.102181
5. Lv J, Wang H, Cheng X, et al. AAV1-hOTOF gene therapy for autosomal recessive deafness 9: a single-arm trial. 2024. The Lancet. https://doi.org/10.1016/S0140-6736(23)02874-X.