Editorial

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Breaking the silence: gene therapy offers hope for OTOF-mediated hearing loss, editorial

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Deafness presents a significant global public health concern, affecting ~1 in 500 newborns, and its prevalence is expected to increase notably[1]. Worldwide, over 1.5 billion people encounter some degree of hearing loss, with about 30 million cases linked to genetic factors in children[2]. Among these genetic causes, an OTOF gene mutation is responsible for deafness in roughly 200 000 individuals globally. Specifically, the mutation results in autosomal recessive deafness 9 (DFNB9), which contributes to 2–8% of all cases of congenital genetic deafness[3,4].

The OTOF gene is responsible for encoding the otoferlin protein, which is synthesized by inner hair cells (IHCs) located within the cochlea. In the cochlea, sound waves undergo conversion into electrical signals by nerve cells, which are then transmitted to the brain for interpretation as sound. Otoferlin plays a crucial role in facilitating the transmission of these signals by interacting with calcium, SNAP25, and Synataxin-1 to facilitate the exocytotic release of glutamate, an excitatory neurotransmitter. Without otoferlin, although sound is converted into electrical signals, they fail to reach the brain for processing[5,6].

At present, there are currently no approved pharmacological interventions available for individuals affected by OTOF-mediated hearing loss. Cochlear implants stand as the primary recommended treatment for individuals diagnosed with DFNB9, especially those experiencing severe to profound deafness[7]. Despite its effectiveness in partially restoring hearing, cochlear implants have limitations, resulting in poorer hearing compared to natural hearing. These limitations include challenges with tone recognition, difficulties in processing intonation, and an inability to fully appreciate music[8]. Hence, there remains a pressing need for alternative treatments to achieve a more natural hearing experience.

Gene therapy specifically targeting OTOF gene-related hearing loss represents a promising avenue in the quest to address this specific genetic form of auditory impairment. Although gene therapy for OTOF-mediated hearing loss is still in the experimental stages, preclinical studies have shown encouraging results in animal models, demonstrating the potential of this approach to restore auditory function[9,10].

HIGHLIGHTS

- Deafness, a global concern, affects millions with genetic factors contributing significantly.
- OTOF gene mutation (DFNB9) is responsible for a notable portion of congenital genetic deafness cases.
- Gene therapy targeting OTOF gene shows promise in restoring auditory function.
- Clinical trial using AAV1-hOTOF gene therapy in children with DFNB9 demonstrates significant hearing recovery.
- Therapy exhibits a favorable safety profile, marking a significant breakthrough in addressing genetic deafness.

Given the encouraging results in the preclinical studies, a single-arm, single-center trial was conducted to study the safety and efficacy of gene therapy with an adeno-associated virus (AAV) serotype 1 carrying a human OTOF transgene (AAV1-hOTOF) as a treatment for children with DFNB9[11]. The trial enrolled six children with confirmed mutations in the OTOF gene, who were administered a single injection of AAV1-hOTOF into the cochlea. One child received a dose of 9×10^{11} vector genomes (vg) whilst the other five received $1{\cdot}5\times10^{12}$ vg.

AAV-mediated gene therapy has emerged as a highly promising approach for treating monogenic inherited disorders, leading to the approval of several AAV gene therapy products by the US FDA. However, despite its success, there hasn't been an AAV product specifically designed for treating deafness. This challenge arises from the size of the human full-length OTOF gene, which exceeds the packaging capacity of AAV. To address this limitation, dual-AAV delivery strategy of splitting the OTOF gene into two and inserting them into two AAV vectors was utilized[12].

The trial showcased encouraging results. Out of the 6 enrolled, five demonstrated hearing recovery, indicated by a substantial reduction (40–57 dB) in average auditory brainstem response (ABR) thresholds across frequencies (0.5–4.0 kHz). The participant receiving a dose of 9×10^{11} vg showed progressive improvement in ABR thresholds, with levels improving from over 95 dB at baseline to 68 dB, 53 dB, and 45 dB at 4, 13, and 26 weeks, respectively. Meanwhile, four children receiving $1{\cdot}5\times10^{12}$ AAV1-hOTOF demonstrated improvements from over 95 dB at baseline to 48, 38, 40, and 55 dB at 26 weeks. These improvements were associated with enhanced speech perception in participants with recovered hearing.

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The safety profile of the therapy was satisfactory, with no observed dose-limiting toxicity or life-threatening adverse effects. However, Grade 1 and 2 events, such as fever, increased lactate dehydrogenase, decreased hemoglobin, decreased fibrinogen, and increased activated partial thromboplastin time, were predominantly reported. Additionally, there were only two instances of decreased neutrophil count in one participant (Grade 3), while no other major adverse events were noted.

In summary, the trial's success in using gene therapy to treat OTOF-mediated hearing loss is a significant breakthrough. The observed hearing recovery in children with DFNB9, along with the therapy's favorable safety profile, marks a promising step forward in addressing genetic deafness. While cochlear implants remain a primary option, gene therapy offers hope for a more effective and natural solution. Further research into its long-term effects and accessibility is essential, but these findings hold great promise for improving the lives of individuals with genetic deafness globally.

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