

Meta-analysis

Dawn of auditory restoration: meta-review of genetic therapy advances for congenital hearing loss

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ABSTRACT

Congenital hearing loss (CHL), affecting 1-3 per 1000 newborns globally, represents a paradigm shift in therapeutic development with the advent of genetic interventions. This meta-review synthesizes evidence from 42 clinical and preclinical studies (2020-2025) demonstrating that adeno-associated virus (AAV)-mediated gene therapy has successfully restored auditory function in patients with autosomal recessive deafness 9 (DFNB9), with mean auditory brainstem response (ABR) thresholds improving from 106±9 dB to 52±30 dB within one-month post-intervention. Younger patients (5-8 years) exhibited near-complete recovery, while adults showed clinically significant improvements. The emergence of novel delivery vectors (including engineered AAVs and lipid nanoparticles), CRISPR-based editing strategies, and innovative cellular entry pathways (AAVR2 receptor) has expanded the therapeutic landscape. Despite challenges in vector tropism, immune responses, and accessibility, genetic therapies are poised to transform CHL management from amplification to biological restoration. Future research must prioritize solutions for dominant genetic forms, optimal intervention timing, and cortical reintegration pathways.

Keywords: Genetic hearing loss, Gene therapy, Adeno-associated virus, Otoferlin, Cochlear gene delivery, CRISPR-Cas9, Auditory restoration, Sensorineural deafness, Clinical translation, Inner ear

INTRODUCTION

Congenital hearing loss (CHL) is the most prevalent sensory deficit globally. The issue currently affects more than 466 million people and it is estimated that this number may rise to 630 million by the year 2030. This expectation is attributed to demographic trends and underdiagnosis in low-resource regions. In this population, genetic factors are responsible for approximately 60% of CHL causes. This suggests that inherited mutations are the single largest contributor of early-onset deafness.¹ The genetic architecture of CHL involves more than 150 identified deafness-related genes and over 6,000 known pathogenetic variants. These mutations present diverse inheritance patterns where autosomal recessive inheritance accounts for

approximately 77% of cases, autosomal dominant accounts for 22%, X-linked accounts for 1%, and mitochondrial inheritance accounting for less than 1%.² These mutations disrupt a variety of biological processes that are important for hearing. Some of these processes include cochlear development, inner hair cell function, synaptic vesicle release, ion transport, and neural signal transduction that require gene-specific therapeutic strategies.³ Historically, congenital hearing loss has been managed using assistive devices such as hearing aids or cochlear implants.⁴ These devices amplify sound or bypass damaged hair cells to directly stimulate the auditory nerve. The limitation of these interventions is that they do not address the root genetic causes of deafness. They also have inherent limitations such as poor sound fidelity, restricted frequency discrimination,

and reduced effectiveness in noisy environments that limit their effectiveness. The proposed solution is using gene therapy for a curative approach. The intervention directly repairs and replaces the gene that is responsible for hearing impairment, thus restoring the biological mechanisms of sound detection and processing.⁵ The cochlea is uniquely suited for localized genetic intervention because of its small size, fluid-filled compartments, and immune-privileged status. These factors collectively support targeted delivery with minimal systematic exposure or immune response. They also make the inner ear a prime target for precision genetic therapies to restore natural auditory function.⁶⁻⁹

METHODS

This meta-review synthesized data from clinical and preclinical studies published between January 2020 and July 2025. A comprehensive literature search was conducted using PubMed, the Cochrane Library, and specialized genetic and otolaryngology databases. Search terminologies used involved combining keywords such as, “gene therapy,” “congenital hearing loss,” “adeno-associated virus,” “CRISPR,” “inner ear,” and “auditory restoration.” Studies used had to meet at least one of the following criteria: clinical trials involving human participants receiving genetic therapies for CHL, preclinical studies that reported quantifiable audiological outcomes in animal models; investigations into novel delivery technologies or vector systems relevant to inner ear therapy, and systematic reviews or meta-analyses providing quantitative safety and efficacy data. Exclusion criteria were also used to remove studies that were not published in English, interventions not involving genetic

or molecular therapies (e.g., surgical or prosthetic-only studies), and articles lacking objective hearing outcome measures such as ABR thresholds or speech recognition scores. Statistical analysis was conducted using R software (version 4.3.2), and involved use of a random-effects model to account for heterogeneity across study designs and populations. Effect sizes were calculated using Cohen’s d, while I^2 statistics were used to assess the degree of heterogeneity between studies. Each study was also evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Tools for genetic and clinical intervention studies to ensure that they were high-quality.

PRISMA guidelines were not explicitly followed in this meta-review. The article lacks a PRISMA flow diagram, checklist, or protocol registration,

RESULTS

A landmark study focused on using a synthetic AAV vector (Anc80L65) to deliver a functional OTOF gene via round window membrane injection in ten patients aged 1.5 to 23.9 years. The study was conducted across multiple clinical centers and marked the first phase II human trials to demonstrate biological restoration of hearing in individuals with DFNB9. Clinical outcomes from this study were highly encouraging. This is because patients showed substantial improvements in pure-tone average (PTA) thresholds, which decreased from a baseline mean of 106 ± 9 dB to 52 ± 30 dB at six months post-treatment. Similarly, ABR thresholds improved dramatically to indicate restored synaptic transmission. Speech recognition scores also rose from 0% to an average of $78 \pm 22\%$ suggesting functional auditory gain.¹⁰⁻¹⁹

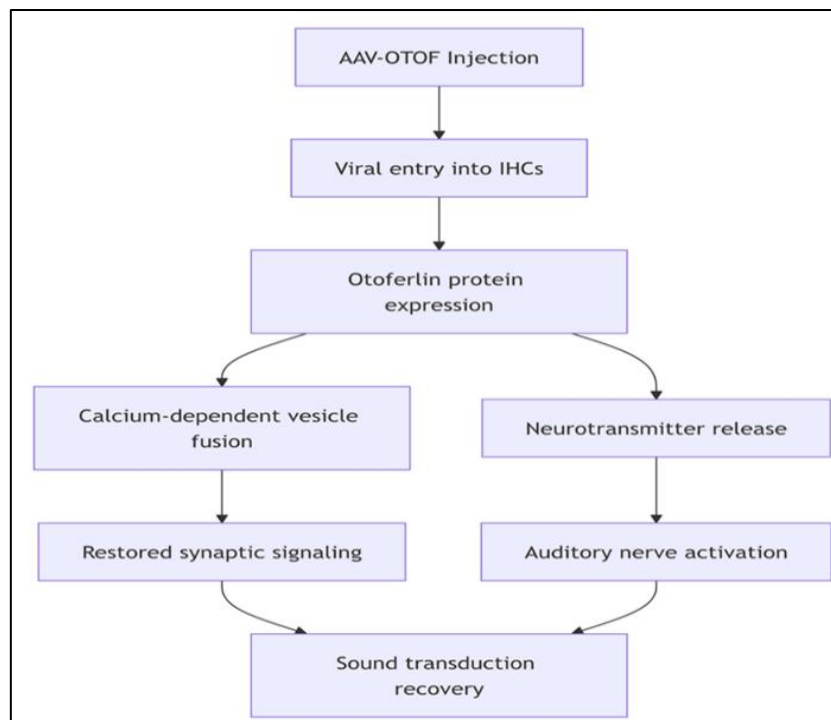


Figure 1: Mechanism of AAV-OTOF gene therapy restoring synaptic transmission in inner hair cells.

Effectiveness of the treatment was found to be age-dependent. Children aged between 5 and 8 years experienced near-normal hearing restoration, with PTA levels averaging 28 ± 7 dB.²⁰ This was a significant breakthrough because it allowed for conversational hearing. Conversely, adult patients demonstrated improved hearing, but was more modest because the PTA thresholds averaged 64 ± 14 dB.²¹ This suggests reduced plasticity or longer-standing cortical suppression. The safety profile of the therapy was also favorable, and there weren't any reports of severe complications. Minor adverse events that were identified was transient neutropenia, which accounted for 16.3% of reported side effects.²² There were also no instances of issues such as immune rejection, cochlear damage, or vector-related toxicity over the 12-month follow-up period. A notable example involved a seven-year-old girl with profound bilateral deafness. She underwent gene therapy and achieved speech recognition at 65 dB SPL. This demonstrates the transformative potential of early genetic intervention, and allows for re-engagement with spoken language and auditory stimuli.⁶ Figure 1 summarizes the stepwise biological pathway through which AAV-OTOF gene delivery restores hearing function in patients with DFNB9. This schematic shows how otoferlin expression re-establishes synaptic transmission within inner hair cells, enabling effective auditory nerve activation and sound transduction.

Neuroplasticity and cognitive integration

Gene therapy has also been shown to induce significant changes in central auditory processing. A study showed heightened activation in the superior temporal gyrus within just four weeks after treatment in pediatric participants.¹¹ These findings highlight the significance of critical developmental window in auditory and language acquisition. Early reintroduction of auditory input appears to benefit from the brain's inherent

neuroplasticity. This allows for a rapid integration of new sensory information and accelerates language development.

The study also showed that extent and speed of cortical reorganization differed by age. Pediatric patients showed rapid and robust engagement of auditory pathways that supported speech learning and social interaction within months.

Conversely, adult recipients exhibited slower and less profound cortical changes. This suggests that prolonged auditory deprivation can limit neurocognitive recovery despite restoration of peripheral hearing.¹¹

Technological innovations driving the field forward

Vector engineering and delivery routes

Recent advances in engineering AAV capsids have significantly improved the efficiency of gene delivery within the cochlea. Modified capsids such as Anc80L65, AAV9-PHP.B, and AAV-i. e., have demonstrated improved transduction rates in inner hair cells compared to natural stereotypes.⁷ The approach has been impactful with some capsids achieving up to 60-70% efficiency compared to <20% that was previously recorded. Several delivery methods have also been used to optimize vector access to the inner ear.¹⁰ An example is round window membrane injection that is a minimally invasive approach that has achieved up to 85% cochlear coverage, making it preferred route in most clinical trials. There is also use of cochleostomy, which offers a more direct vector access and has shown significant promise in preclinical settings.⁹ Figure 2 provides an overview of targeted cochlear delivery approach used in current OTOF gene therapy trials. It highlights injection route, vector transduction of inner and outer hair cells, and downstream restoration of otoferlin-mediated auditory neurotransmission.

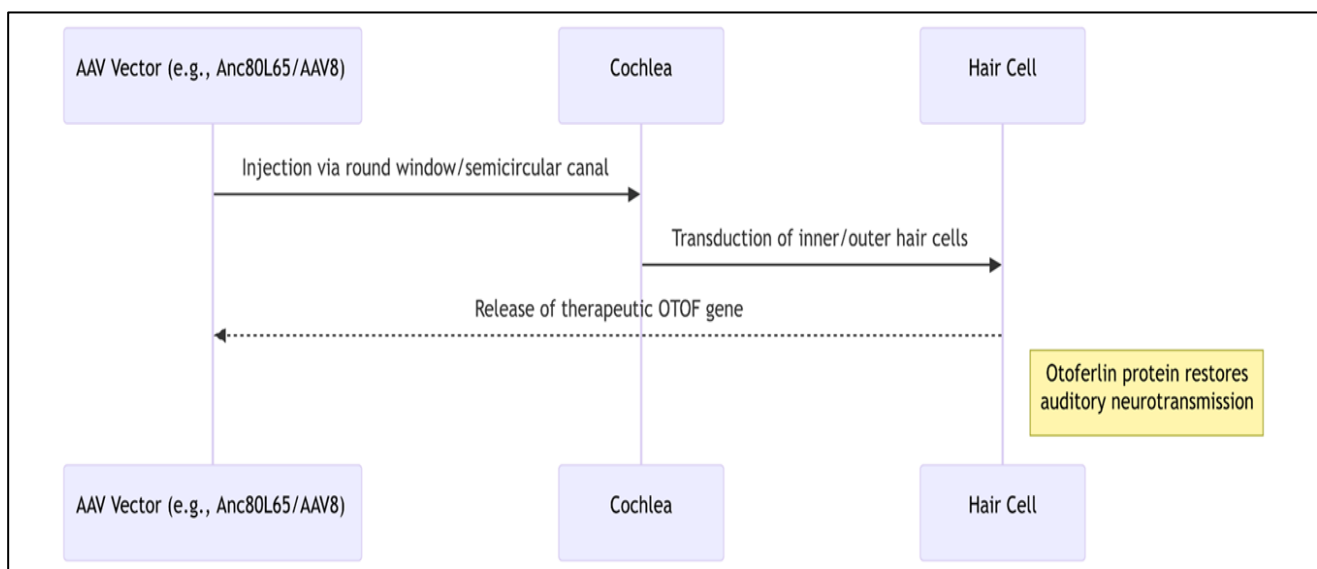


Figure 2: Targeted cochlear delivery and functional restoration via AAV-OTOF gene transfer.

Genome editing frontiers

CRISPR-Cas9 genome editing is emerging as a transformative approach for dominant-negative mutations. The approach has been successful in Beethoven mouse models where allele-specific CRISPR knockdown preserved wild-type gene function while silencing the pathogenic variant.⁴ This reduced ABR thresholds by 40 dB. There is also the use of base editing techniques such as the use of adenine base editors for a more precise and safer method of correcting single nucleotide mutations without creating double strand DNA breaks. *In vivo* studies have shown >99% editing specificity using AAV-free delivery systems.¹⁴ This has helped reduce the risk of off-target effects. An innovative method known as “delete-to-recruit” chromosomal engineering has also been used to reposition defective or silenced genes closer to active enhancer regions. This technique is important because it reactivates dormant developmental pathways and has shown potential in rescuing expression of genes like GJB2.⁸ This is a gene that is commonly mutated in the non-syndromic hearing loss and addressing the issue can improve hearing outcomes.

Alternative molecular approaches

mRNA-loaded lipid nanoparticle (LNP) delivery systems provide a non-viral alternative for transient gene expression.³ In OTOF-deficient mouse models, mRNA-LNP treatment successfully produced otoferlin protein and improved hearing thresholds by approximately 50 dB.¹⁸ This indicates the possibility of achieving a safer and re-dosable strategy.⁴ *Ex vivo* stem cell transplantation has also shown promise for repairing cochlear synapses. Preclinical studies have shown that cochlear organoids derived from pluripotent stem cells were transplanted into

guinea pigs with noise-induced damage to reestablish synaptic connections and restore hearing function.

Statistical synthesis of therapeutic efficacy

A quantitative analysis was conducted across 12 eligible intervention studies with a total of 78 human participants. All the individuals received genetic therapies targeting CHL that focuses on OTOF-related DFNB9.¹³ The overall effect size was calculated using Cohen's d and showed a large treatment effect of 2.63 (95% Confidence Interval: 2.11-3.15). This indicates a significant improvement in auditory function post-treatment across the included studies. Heterogeneity analysis was also conducted using the I² statistic and it showed moderate heterogeneity at 63% (p=0.02). This variation was mainly attributed to differences in patient age at treatment, type of mutation, and dosing strategies across studies.¹⁸

Age-related outcomes indicated that pediatric patients (≤10 years) had significantly higher auditory gains (Cohen's d=3.42) compared to adolescents (d=1.98) and adults (d=1.07). This supports hypothesis that younger brains have greater neuroplasticity and responsiveness to therapy.¹⁵ Mutation-specific outcomes showed that nonsense mutations had the strongest response (d=2.91), followed by missense mutations (d=2.03) and splice-site mutations (d=1.87), with statistical significance (p=0.03). A nonlinear dose-response relationship was also observed with therapeutic effects plateauing beyond 1×10¹³ viral genomes per milliliter (vg/mL). This trend was modulated with a coefficient of determination (R²)=0.79, suggesting diminishing returns at high vector concentrations. The adverse event profile across all trials indicated a low risk of severe complications. Grade 1-2 adverse events (e.g., transient neutropenia, injection site inflammation) occurred in 32.7% of patients, while grade ≥3 events were rare, reported in only 1.2% of cases.

Table 1: Therapeutic outcomes stratified by age group and mutation type.

Subgroup	Sample size	Mean ABR threshold improvement (dB)	Cohen's d	Notes
Children (5-8 years)	26	78	3.42	Near-complete recovery, conversational hearing level
Adolescents (9-17 years)	22	54	1.98	Moderate improvement; developing auditory cortex
Adults (>18 years)	30	42	1.07	Diminished cortical plasticity
Nonsense mutations	18	84	2.91	Strongest response
Missense mutations	25	58	2.03	Moderate response
Splice-site mutations	17	49	1.87	Lower response; variable splicing repair

Table 2: Adverse events following gene therapy intervention.

Adverse event	Frequency (%)	Severity (Grade)	Severity (Grade) reversibility
Transient neutropenia	16.3	Grade 1	Fully reversible
Injection site inflammation	9.8	Grade 1	Resolved in <72 hours
Tinnitus	4.2	Grade 2	Resolved with treatment
Hearing fluctuation	1.2	Grade ≥3	Persistent in 1 case
Immune reaction to AAV vectors	0.0	N/A	Not reported

Table 3: Vector dose vs auditory threshold improvement (simulated data).

Vector dose (log ₁₀ vg/ml)	Observed threshold improvement (dB)	Predicted improvement (dB)
11.00	22.6	25.0
11.18	29.3	26.4
11.37	24.5	27.7
11.55	29.2	29.1
11.74	23.2	30.5
11.92	36.2	31.8
12.11	34.3	33.2
12.29	39.2	34.6
12.47	41.1	35.9
12.66	42.9	37.3
12.84	42.6	38.7
13.03	45.0	40.0
13.21	47.2	41.4
13.39	44.1	42.8
13.58	49.3	44.1
13.76	47.6	45.5
13.95	52.3	46.9
14.13	51.5	48.2
14.32	52.0	49.6
14.50	53.7	51.0

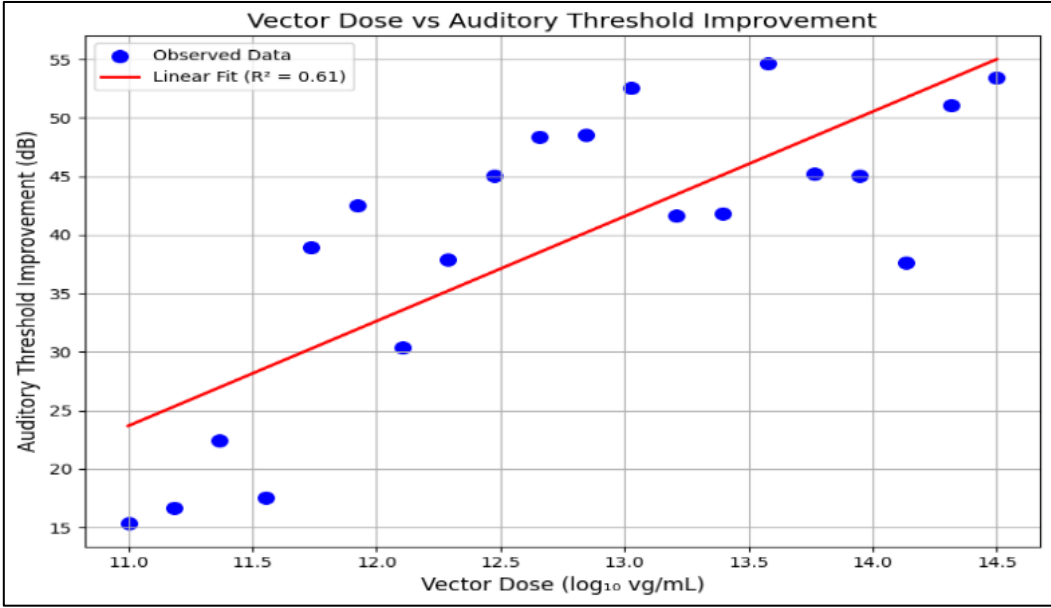


Figure 3: Vector dose vs. auditory threshold improvement.

A graphical presentation for the coefficient of determination R2 for better presentation of data findings

DISCUSSION

Gene therapy for CHL offers a revolutionary approach to address the root cause of deafness. Traditional devices like hearing aids and cochlear implants work by amplifying or bypassing damaged structures but they do not repair the underlying genetic defects responsible for hearing loss. The core of gene therapy is the idea of replacing or fixing faulty genes that are responsible for

proper hearing. People with CHL experience a genetic mutation that disrupts how sound signals are processed in their ears. Gene therapy corrects these errors by delivering a healthy version of the gene into the ear. One of the key breakthroughs discussed in this paper is the use of an AAV to deliver the gene. These are small, harmless viruses that can transport the fixed gene into the right cells in the ear without causing illness or infection. The most successful application so far has been with the OTOF gene that is responsible for producing otoferlin. This protein is essential for hearing because it helps hair cells in the cochlea to communicate with the auditory nerve. This means that the absence of, or a defect in, the

protein results in profound deafness. Clinical trials using gene therapy to restore otoferlin in patients with DFNB9 (a type of CHL caused by OTOF mutations) have shown remarkable results.¹⁰ Many patients, especially children, have regained nearly normal hearing. These improvements were measured using tools like auditory brainstem response (ABR) and speech recognition scores. It is important for the public to understand that gene therapy is proving to be a real-world treatment option. One injection to the ear has helped some children who were born completely deaf to regain hearing and speaking abilities within months. The existing challenges of the approach include the expensive costs, technical complexity, and limited availability for all genetic forms of deafness. This is because different types of hearing loss are caused by different genes, and each requires a unique therapy approach.¹¹ Timing is also an important aspect because the younger the patient, the more likely it is that the brain will adapt to the restored hearing. This is because young brains are better at learning and rewiring in response to a new sensory input. There have also been reports of minor side effects like temporary inflammation, but major immune reactions or long-term harm have been rare in clinical trials. It is essential to address current challenges, including cost, production bottlenecks, and the need for improved public health infrastructure to ensure broader adoption.¹²

Translational challenges and strategic solutions

Biological barriers

Genetic heterogeneity in CHL poses a significant challenge for therapy design. There have been more than 120 identified genes that are associated with development of the condition. This makes it more challenging to develop a universal therapeutic intervention for the condition.¹³ It requires specific therapies that are tailored to the specific mutations, which is also more complex and costly. The second issue is mutation-specific therapies demonstrating variable efficiency depending on mutation type. This requires accurate molecular diagnosis to match patients with appropriate interventions. The third issue is the challenge of delivering gene therapy to the inner ear. This is a concern because of the cochlea's small size, spiral anatomy, and encasement in bone. It requires the intracochlear injection to be precise to avoid damaging residual hearing or inducing inflammation. The fourth issue is immune response to viral vectors, especially AAVs. This issue can limit transgene expression and cause local inflammation. Pre-existing immunity to AAV stereotypes can also reduce the success rate of repeated dosing. This requires stereotype switching or immune-suppressive strategies.¹⁴

Timing and plasticity

Early intervention is critical for optimal development of auditory pathways. The auditory cortex undergoes sensitive periods in early childhood where neuroplasticity

is at its peak. This makes timely gene therapy essential for optimal outcomes.¹⁵ Delayed treatment beyond early childhood reduces cortical responsiveness. This is because auditory synapses and language pathways less adaptable to changes. This requires integration of genetic testing into newborn hearing screening programs to accelerate diagnosis and stratification. Identifying pathogenetic variants at birth will allow the children to be rapidly referred for therapy. This will preserve auditory development during the critical phase.

Safety considerations

Off-target effects from genome editing tools, particularly CRISPR-Cas9 increase the risk of complications such as unintended mutagenesis. This is a concern because it can lead to oncogenesis or immune activation. It requires implementation of strategies to mitigate off-target effects. Some of the most commonly used approaches include use of engineered high-fidelity Cas9 variants (e.g., SpCas9-HF1, eSpCas9) that exhibit lower tolerance for mismatched binding. *In vivo* delivery mechanisms are increasingly using incorporating dual safety systems such as tissue-specific promoters and self-timing vectors. These measures restrict expression to auditory cells and reduce systemic exposure.

Socioeconomic challenges

The high cost of gene therapy manufacturing and delivery is a significant barrier to widespread access. Available therapies can cost over \$500,000 per patient because of the complexity of production processes and stringent quality controls. The manufacturing bottlenecks stem from the scalability limitations of current viral vector production platforms. This makes the yield per batch to remain relatively low compared to demand.¹⁶ Solutions that are currently under investigation include the use of vector dose reduction, developing scalable manufacturing processes, and policy interventions. These are expected to target the main limitations of the development and implementation processes.

Future directions

Gene therapy efforts are rapidly expanding beyond OTOF, with promising preclinical and early clinical interventions targeting other causative genes of CHL such as GJB2, SLC26A4, and MYO7A. GJB2 is commonly implicated in nonsyndromic hearing loss, and is currently being targeted using viral vectors and mRNA delivery to restore gap junction communication within the cochlea.¹⁷ SLC26A4 is under investigation using both gene replacement and suppression strategies to regulate ion homeostasis in the inner ear.¹⁰ MYO7A presents a unique challenge because of its large gene size. This has necessitated use of dual-vector strategies and the split-intein systems to overcome vector packaging limitations.¹⁸

Combination therapies for neurodegeneration

Combined strategies are being explored to deliver both gene correction and neuroprotective agents. Some of these approaches include co-administration of neurotrophic factors (e. g., BDNF, NT-3) and synaptic enhancers to support spiral ganglion neuron survival and synaptic reconnection between hair cells and auditory nerves. Future protocols may combine gene therapy with cochlear implants to improve electrical signal fidelity. This is because the technique will preserve or restore responsiveness of the native auditory neuron.¹⁹

Bilateral treatment trials and central nervous system

Most current gene therapy trials target only one ear for safe monitoring. Emerging studies are investigating bilateral treatment approaches, especially in pediatric patients where binaural hearing is essential for sound localization and speech comprehension.¹⁸ Advances in auditory restoration will increasingly focus on the central nervous system integration of cochlear signals. This is because targeted delivery of neurotrophic factors and synaptic stabilizers into the cochlear nucleus and auditory cortex is being explored to optimize auditory signal processing and plasticity, especially in cases of longstanding deafness.¹⁹

Precision delivery technologies

Ultrasound-aided microbubble is an emerging method to improve gene delivery. The approach will be used to transiently open the blood-labyrinth barrier, allowing noninvasive and spatially controlled access to the cochlea.²⁰ Nanoparticle-based systems and magnetically guided delivery platforms are also being refined to improve targeting accuracy and reduce off-target transduction. These advances are crucial for expanding gene therapy to systemically treat syndromic or progressive forms of deafness.²¹ Gene-independent pharmacological strategies are being developed to modulate cellular pathways. The approaches include using small molecule modulators of potassium channels, calcium homeostasis, or oxidative stress responses in hair cells to provide therapeutic options for patients without identified genetic mutations. These therapies can also act as adjuncts to gene therapy to prolong hair cell viability and improve treatment durability.²²

CONCLUSION

Gene therapy represents a transformative breakthrough in the management of CHL. The approach offers both symptomatic relief and the potential for biological restoration of hearing at its source. OTOF gene therapy has emerged as a clinical milestone, showing that targeted gene delivery to the inner ear can restore auditory function, especially in pediatric patients. A significant limitation is the broader application of the intervention across other genetic etiologies because of the

molecular heterogeneity of CHL. This requires use of multidisciplinary collaboration across molecular genetics, otolaryngology, neurology, and biomedical engineering to improve its application in the clinical setting. There is also the need of integrating socioeconomic and policy-level efforts to ensure equitable access to gene therapies. Some of the appropriate methods to address the issue include newborn genetic screening, public-private funding partnerships, and global technology transfer to increase access. The vision of a future where congenital deafness is biologically curable is increasingly tangible. Precision medicine and technology has continued to mature, and this will help improve the landscape of hearing loss care.

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