Pharmacology and Therapeutics

Inner-Ear Gene Therapy for Hereditary Hearing Loss: A PubMed-Based Scoping Review of Published Human Studies and the Clinical Trial Registry Landscape

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Abstract

Objectives

Gene therapy for hereditary hearing loss has entered early clinical translation, but human evidence remains limited. This scoping review mapped published human evidence and situated it within the broader clinical trial landscape.

Methods

Following PRISMA-ScR, PubMed was searched on April 17, 2026, for peer-reviewed human studies of therapeutic gene transfer for hereditary hearing loss published from 2015 to 2026. Restriction to one bibliographic database is acknowledged, and the review is framed as a PubMed-based scoping review rather than a comprehensive multi-database synthesis. ClinicalTrials.gov, ICTRP, ChiCTR, and CTIS were also searched. Records were manually screened and deduplicated across registries. A primary reviewer screened titles and abstracts, and a second reviewer verified all full-text and registry inclusion decisions.

Results

PubMed yielded 129 records, of which six studies from three independent clinical programs were included. All targeted OTOF-related deafness using intracochlear dual-vector AAV systems. Three publications represented 11 unique participants from ChiCTR2200063181; two Otovia publications (NCT05901480) reported overlapping cohorts; and one publication reported the DB-OTO trial (NCT05788536). Overall, the evidence represented approximately 33 unique participants, not the publication-level total of 46. Auditory outcomes generally improved, but reporting was heterogeneous and follow-up was short. Registry searches yielded 632 raw records and nine unique interventional trials after screening and deduplication. Eight targeted OTOF, one targeted GJB2, and none targeted TMC1.

Conclusions

Published evidence remains confined to early-phase studies of a single genetic subtype, whereas registry data indicate a broader, evolving landscape. Generalizability, target imbalance, and long-term safety remain unresolved.

Keywords: gene therapy, hereditary hearing loss, OTOF, otoferlin, adeno-associated virus, scoping review

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1. INTRODUCTION

Hereditary hearing loss presents a fundamental challenge for therapeutic development: a single clinical phenotype arises from a highly heterogeneous set of genetic and biological mechanisms. More than 150 genes have been implicated in hereditary hearing loss, encompassing both syndromic and nonsyndromic forms.[1] This heterogeneity directly defines the boundaries of therapeutic feasibility, because interventions that are mechanistically effective for one genetic subtype may be entirely irrelevant for another, and the degree to which cochlear architecture is preserved at the time of intervention determines whether any form of gene replacement can succeed.

The dominant clinical solution to sensorineural hearing loss, cochlear implantation, sidesteps this complexity by bypassing dysfunctional cochlear structures altogether. Rather than restoring physiological hearing, a cochlear implant converts sound into electrical signals delivered directly to the auditory nerve. In appropriately selected patients, this approach provides meaningful functional benefit, particularly for speech understanding in quiet environments. Outcomes are highly variable and depend on factors including residual neural integrity, age at implantation, duration of auditory deprivation, and rehabilitation intensity.[2] Cochlear implantation is compensatory rather than restorative: it does not recreate the rich spectrotemporal coding of the normal inner ear, and it introduces a permanent foreign-body burden into a surgically challenging space. For patients with intact but nonfunctional hair cells, it also sacrifices residual natural hearing that might otherwise be preserved or recovered.

Gene therapy introduces a different therapeutic paradigm by targeting the underlying molecular defect rather than circumventing the affected structure. Advances in adeno-associated viral (AAV) vector engineering over the past decade have enabled increasingly precise delivery of genetic material to the sensory cells of the cochlea, and preclinical studies across multiple genetic models have demonstrated restoration of auditory function that would not be achievable through device-based approaches.[3-5] This strategy offers the potential for physiological recovery rather than compensation, provided that the cellular substrate for such recovery remains viable. The primary barrier to clinical translation has not been conceptual but practical, requiring the development of vectors with sufficient cochlear tropism, packaging capacity for large transgenes, and safety profiles acceptable for use in young children.

Clinical translation has focused almost exclusively on OTOF-related deafness, a form of auditory neuropathy in which mutations in the otoferlin gene impair synaptic vesicle release at the inner hair cell ribbon synapse while leaving the broader cochlear architecture largely intact.[6] This biological profile creates a favorable therapeutic context: hair cells are present, afferent neural connections are functional, and the disease mechanism is localized to a single synaptic protein. Restoring otoferlin expression has the potential to rescue an otherwise intact auditory system, making OTOF-related deafness a logical first target for early-phase human studies. The same cannot be said for many other genetic causes of hearing loss, in which the pathology is more diffuse, structurally destructive, or temporally narrow in its reversibility.

The divergence between what has been studied and what the broader clinical landscape contains is a defining feature of this field. Considered in isolation, the peer-reviewed literature appears narrow: a small number of early-phase studies, all targeting the same gene, with small samples, short follow-up, and no head-to-head comparisons. Clinical trial registries reveal a more active landscape, with nine unique interventional gene therapy trials identified across registries after screening and deduplication at the time of this review. The published literature is therefore a lagging indicator of clinical activity rather than a comprehensive accounting of where the field stands.

This scoping review was designed to address that gap. By systematically mapping the published human evidence alongside the broader registry-derived trial landscape, the review aims to provide an integrated picture of early clinical translation, characterize patterns of target selection and platform development, and clarify the degree to which current findings can or cannot be generalized across the heterogeneous spectrum of hereditary hearing loss. Given the small number of available human studies, early-phase trial designs, and substantial heterogeneity in interventions and outcome reporting, a scoping approach was selected to characterize the structure of the evidence rather than to estimate pooled treatment effects.[7,8]

2. METHODS

This study was conducted as a scoping review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).[9] A scoping approach was selected because the available human literature remains small, methodologically heterogeneous, and dominated by early-phase studies, making evidence mapping more appropriate than pooled effect estimation.[8] No protocol was prospectively registered for this review.

2.1. INFORMATION SOURCES AND SEARCH STRATEGY

2.1.1. PUBLISHED LITERATURE

A structured search of a single bibliographic database, PubMed, was conducted on April 17, 2026, to identify peer-reviewed human studies of therapeutic gene transfer for hereditary hearing loss. The search combined intervention-related terms, disease-related terms, and gene-specific terms. Filters were applied for English language, publication years 2015 through 2026, and human studies. The complete PubMed search string is provided in the Supplementary Material. The decision to restrict bibliographic searching to PubMed is acknowledged as a methodological constraint that may reduce capture sensitivity for studies indexed exclusively in EMBASE, Cochrane CENTRAL, Scopus, Web of Science, or regional databases. The review is

Table 1. Registry Search Strategy and Source Directories

Source	Purpose	Search Terms Used
ClinicalTrials.gov	Primary registry capture	hearing loss gene therapy; deafness gene therapy; cochlea gene therapy; inner ear gene therapy; sensorineural hearing loss gene; cochlear gene therapy; OTOF; otoferlin; DFNB9; GJB2; connexin 26; DFNB1; TMC1; AAV hearing; AAV deafness; AAVAnc80; gene transfer hearing; gene replacement deafness
ICTRP	Supplementary global capture	hearing loss gene therapy; deafness gene therapy; cochlea gene therapy; inner ear gene therapy; sensorineural hearing loss gene; OTOF; otoferlin; DFNB9; GJB2; connexin 26; TMC1; AAV; AAV hearing; gene transfer hearing; gene replacement deafness
ChiCTR (direct)	Chinese registry direct search	OTOF; GJB2; TMC1; otoferlin; deafness gene therapy; hearing gene therapy; Chinese-language equivalents
CTIS (direct)	EU registry direct search	OTOF; otoferlin; GJB2; gene therapy hearing; deafness gene therapy

framed accordingly as a PubMed-based scoping review of the published human evidence rather than as a comprehensive multi-database evidence synthesis, and implications for capture sensitivity are addressed in the Limitations section.

2.1.2. CLINICAL TRIAL REGISTRIES

To account for publication lag and capture ongoing, completed, or unpublished interventional trials not yet represented in the peer-reviewed literature, supplementary searches were conducted across four registry sources: ClinicalTrials.gov (primary structured registry), ICTRP (global capture including ChiCTR and EU registries), the Chinese Clinical Trial Registry (ChiCTR, direct search with English and Chinese-language terms), and the European Union Clinical Trials Information System (CTIS, direct search). Iterative keyword-based strategies were structured across three complementary layers: broad condition-plus-intervention terms, gene-specific terms (OTOF, otoferlin, DFNB9, GJB2, connexin 26, DFNB1, TMC1), and platform-related terms (AAV, AAVAnc80, gene transfer, gene replacement). TMC1-directed searches returned no results in any registry source. The complete registry search strategy is summarized in Table 1.

2.1.3. GREY LITERATURE

Conference proceedings, preprints, and industry communications were not systematically searched. This decision was made to preserve a clear evidentiary distinction between the two primary sources of evidence: peer-reviewed published human studies and formally registered interventional trials. Grey literature sources reflect preliminary, non-peer-reviewed disclosures subject to revision, selective reporting, and incomplete methodological documentation. Their inclusion would have introduced an additional evidence tier with uncertain quality characteristics, complicating the interpretive framework without proportionate gain in coverage given that the principal emerging programs are already captured through their registry records.

2.2. ELIGIBILITY CRITERIA

Published studies were included if they reported original human data, involved therapeutic gene transfer or gene replacement targeting hereditary or genetically defined hearing loss, and reported auditory outcomes including objective measures such as auditory brainstem response (ABR) or pure-tone audiometry (PTA), or functional outcomes such as speech perception. Studies were excluded if they were preclinical, non-human, mechanistic without a therapeutic intervention, limited to diagnostic or genetic characterization, observational, or published as reviews, editorials, or commentaries. Secondary analyses of previously reported patient cohorts that did not report new therapeutic interventions or new primary efficacy endpoints were excluded from the eligible study count but were considered as supporting evidence in the narrative synthesis.

Registry records were included if they represented human interventional gene therapy studies targeting hereditary or genetically defined hearing loss. Records were excluded if they were observational, screening-based, natural history, or mechanistic studies; if they employed therapeutic paradigms outside the scope of gene transfer or gene replacement (neurotrophin delivery and RNA base editing were excluded); or if they represented long-term follow-up extensions of included parent trials without new therapeutic administration. Records identified in multiple registries were removed during cross-registry deduplication using trial identifiers (NCT, ChiCTR, and CTIS codes).

2.3. STUDY SELECTION

The published literature search and the registry screening were conducted as parallel, independent streams and are not merged at any stage of the selection process. Their results are reported separately below.

2.3.1. SCREENING PROCESS AND INTER-REVIEWER AGREEMENT

Title and abstract screening, full-text eligibility assessment, and registry record screening were conducted by the primary author (MA). To address the methodological vulnerability of single-reviewer screening, all inclusion and

Table 2. PubMed Study Selection Flow

Stage	n
Records identified through PubMed	129
Records after duplicate removal	129
Records screened (title and abstract)	129
Records excluded at screening	103
Full-text articles assessed for eligibility	26
Full-text articles excluded	20
Studies included in qualitative synthesis	6

Table 3. Reasons for Full-Text Exclusion

Reason for Exclusion	n
Preclinical-only studies	11
Mechanistic or non-therapeutic investigations	3
Absence of human intervention	2
Absence of reported auditory outcomes	2
Diagnostic or genetic characterization studies	2
Total	20

exclusion decisions at the full-text and registry stages were subsequently reviewed by a second reviewer (see Acknowledgments) against the predefined eligibility criteria, with any disagreement resolved by discussion until consensus was reached. The second reviewer concurred with 26 of 26 full-text decisions and 66 of 69 registry inclusion decisions; the three registry discrepancies, all concerning borderline interpretation of the "long-term follow-up extension of a parent trial" exclusion criterion, were resolved through discussion without third-reviewer adjudication. This verification procedure does not constitute fully independent dual screening, and the absence of dual independent screening at the initial title-and-abstract stage is acknowledged as a residual methodological limitation.

2.3.2. *PUBLISHED EVIDENCE*

The PubMed search yielded 129 records. No duplicates were identified within the database results. All 129 records underwent title and abstract screening, after which 103 were excluded for reasons including irrelevance to human gene therapy for hearing loss, non-English language despite filter application, and topical misalignment (records pertaining to AAV biology in non-auditory systems captured by the broad search terms). Twenty-six full-text articles were assessed for eligibility (Table 2).

Of the 26 full-text articles reviewed, 20 were excluded for predefined reasons. The most common reason for exclusion was a preclinical-only study design, accounting for 11 of 20 exclusions. The remaining nine exclusions were distributed across mechanistic investigations without a therapeutic component, studies lacking a human intervention or reported auditory outcomes, and diagnostic or genetic characterization studies that did not involve gene delivery. The distribution of full-text exclusion reasons is presented in Table 3.

Six studies met all inclusion criteria and were carried forward into the qualitative synthesis. All six reported original human data from therapeutic gene transfer targeting OTOF-related deafness.

2.3.3. *REGISTRY-DERIVED TRIAL LANDSCAPE*

Registry screening was conducted as a separate stream from the published literature pipeline. ClinicalTrials.gov yielded 346 records across 18 keyword queries, which reduced to 120 unique NCT numbers after within-source deduplication. ICTRP yielded 280 records across 15 keyword queries, reducing to 235 unique trial identifiers. Direct CTIS searches contributed 3 unique trial numbers across 2 export files. These raw counts and the results of within-source deduplication are summarized in Table 4. After topic-based filtering to retain only hearing-related records, 56 remained from ClinicalTrials.gov, 28 from ICTRP, and 3 from CTIS, producing a combined pool of 87 hearing-related records prior to cross-registry deduplication. Fifteen ICTRP records were identified as ClinicalTrials.gov duplicates by their NCT prefix, and 3 CTIS records duplicated entries already captured through ClinicalTrials.gov or ICTRP, yielding 69 unique hearing-related records for eligibility screening.

Application of the predefined inclusion and exclusion criteria to the 69 unique hearing-related records resulted in the exclusion of 60 records. The largest category of exclusion was non-interventional study design, which accounted for 37 records and included observational cohorts, natural history studies, patient registries, screening programs, and comparative audiology assessments without a gene therapy component. Fifteen records were excluded because they involved therapeutic interventions outside the scope of gene transfer or gene replacement as defined for this review, including cochlear implant evaluations, pharmacological agents, antisense oligonucleotides, stem cell therapies, and rehabilitation system development. Three records described gene therapy programs targeting conditions other than hearing loss (captured by the broad AAV search terms), and three additional records were resolved as cross-registry duplicates during the screening stage. One record involving RNA base editing for OTOF-related hearing loss was excluded on the basis of the predefined therapeutic paradigm boundary; this record had also been withdrawn by the sponsor. One record was excluded because it represented a long-term follow-up extension of an included parent trial with no new therapeutic administration. The full distribution of exclusion reasons is presented in Table 5.

Nine unique interventional gene therapy trials were retained for descriptive analysis, comprising six identified through ClinicalTrials.gov and three through ChiCTR (captured via ICTRP). No unique trials were contributed exclusively by the direct CTIS search; all CTIS records duplicated entries already captured through ClinicalTrials.gov or ICTRP.

The complete study selection process for both the published literature and registry pipelines is illustrated in Fig-

Table 4. Registry Screening Summary

Registry Source	Records Identified	Unique After Within-Source Dedup	Unique Trials Retained After Full Screening
ClinicalTrials.gov	346	120	6
ICTRP	280	235	3
CTIS direct	6	3	0
Total	632	358	9

Table 5. Reasons for Registry Exclusion (Applied to 69 Unique Hearing-Related Records)

Exclusion Category	n
Non-interventional (observational, natural history, screening, registry, comparative)	37
Wrong therapeutic paradigm (not gene therapy: devices, drugs, ASO, stem cells, rehabilitation)	15
Gene therapy but not for hearing loss	3
Cross-registry duplicates resolved at screening	3
RNA base editing (excluded paradigm; record also withdrawn)	1
Long-term follow-up extension of parent trial (no new intervention)	1
Total excluded	60

ure 1. The left pipeline maps the published evidence identified through PubMed. The right pipeline maps the registry-derived trial landscape identified through ClinicalTrials.gov, ICTRP, ChiCTR, and CTIS. The two pipelines were conducted as independent, parallel streams and are not merged at any stage. Registry records were screened manually to account for heterogeneity in record structure and indexing practices across member registries, and cross-registry deduplication was performed using trial identifiers (NCT, ChiCTR, and CTIS codes) to ensure that records registered in multiple systems were counted only once. A complete registry audit trail, listing the unique hearing-related records screened at the eligibility stage with trial identifier, source registry, title, intervention, gene target, recruitment status, and inclusion/exclusion decision with reason, is provided as Supplementary File 1.

2.4. DATA CHARTING, EXTRACTION, AND SYNTHESIS

For included published studies, data were extracted on publication year, country of origin, study design, sample size, age range, gene target, vector or platform type, delivery route, follow-up duration, auditory outcomes, and adverse events. Where multiple publications drew from the same trial registration, patient-level overlap was documented. For registry-derived trials, extracted variables included trial identifier, registry source, therapy designation, gene target, platform type, and recruitment status. Registry records were used descriptively and were not treated as equivalent to peer-reviewed efficacy evidence. Given the small number of published studies and heterogeneity of designs and outcome measures, results were synthesized narratively. Consistent with scoping review methodology, formal risk-of-bias assessment was not performed. The data charting form was piloted on the first two included publications and adjusted iteratively before being applied to the remaining studies and to the registry-derived dataset.

3. RESULTS

3.1. PUBLISHED HUMAN EVIDENCE

Clinical translation of OTOF-targeted gene therapy into human trials was supported by a substantial preclinical foundation, including AAV-mediated restoration of auditory function in mouse models of both TMC1-related genetic deafness and otoferlin-knockout deafness using single and dual-AAV delivery strategies.[3-5] The six included studies are summarized in Table 6. All six targeted OTOF-related deafness, all employed AAV-based dual-vector systems to accommodate the approximately 6-kb OTOF coding sequence (which exceeds the approximately 4.7-kb packaging capacity of standard single AAV vectors[10]), and all used intracochlear delivery routes. Sample sizes ranged from 2 to 12 participants per study, and all interventional designs were single-arm, with the exception of one nonrandomized comparative cohort.

Three publications (Lv et al, Wang et al, and Cheng et al) drew participants from a single trial registration (ChiCTR2200063181) conducted at the Eye and ENT Hospital of Fudan University using the same AAV1-hOTOF dual-vector product. Lv et al reported the first six participants (unilateral injection)[11]; Wang et al reported five additional participants enrolled after a protocol amendment permitting bilateral administration[12]; and Cheng et al reported the gene therapy arm of a nonrandomized comparison at extended follow-up using the same 11 participants.[13] The total number of unique participants across these three publications is therefore 11, not 22. Two further publications (Qi et al 2024 and Qi et al 2025) report sequential cohorts

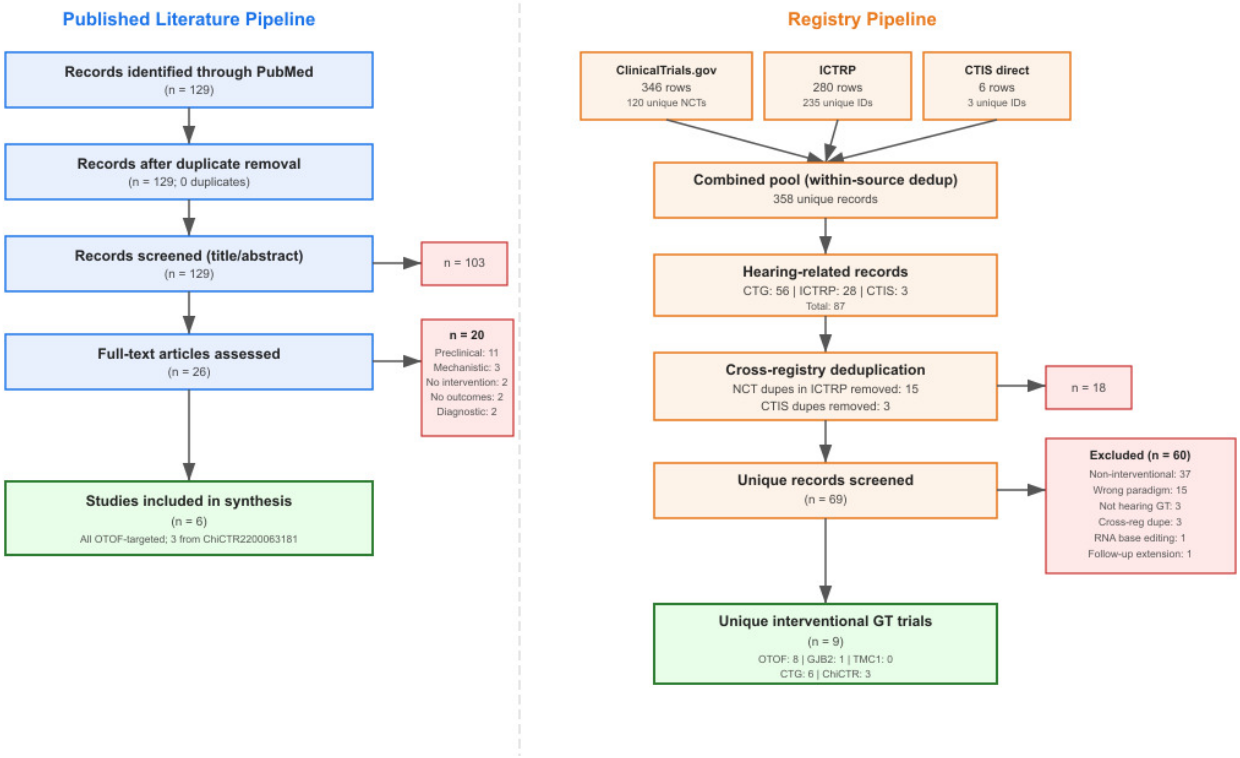

Figure 1. PRISMA 2020 flow diagram for a scoping review of published human studies and the clinical trial registry landscape in inner-ear gene therapy for hereditary hearing loss.

Note: The two pipelines were conducted as parallel, independent streams and are not merged. Registry records were screened manually and deduplicated using trial identifiers (NCT, ChiCTR, CTIS codes). All searches conducted April 17, 2026. TMC1 searches returned no results in any source. ICTRP = International Clinical Trials Registry Platform; CTG = ClinicalTrials.gov; CTIS = Clinical Trials Information System; GT = gene therapy. Three CTIS records were cross-registry duplicates of ClinicalTrials.gov entries and contributed zero unique trials to the final dataset.

from a separate single-arm trial (NCT05901480) conducted by Otovia Therapeutics Inc. using a dual AAV-OTOF (Anc80L65 capsid) product; the 2024 case series describes the first two participants[14] of the cohort subsequently expanded to ten participants and reported in 2025.[15] The unique participant count across these two publications is therefore 10, not 12. The remaining publication (Valayannopoulos et al 2026) reports the DB-OTO trial (NCT05788536, Regeneron/Akouos)[16] and contributes 12 unique participants with no overlap with the other programs.

3.2. PLATFORM-LEVEL CONSIDERATIONS

All six studies employed dual-AAV vector systems, in which the OTOF transgene is split across two AAV particles that recombine intracellularly. Within this shared framework, programs differed in capsid selection and promoter strategy. The approaches are summarized in Table 7.

3.3. CLINICAL OUTCOMES

Across all six studies, auditory improvement was consistently observed. This directional consistency is the most robust finding in the current evidence base, but it must be interpreted against the patient-overlap structure described above: three of six publications draw from a single trial cohort, so the apparent convergence is partly mechanical. In the earliest published trial, ABR thresholds improved by approximately 40 to 57 dB at 26 weeks.[11] Subsequent reports showed clinically meaningful auditory gains, although different outcome measures were used. Wang et al reported that ear-specific average ABR thresholds, >95 dB in both ears at baseline, ranged from 50 to 85 dB at the latest reported assessment (26 weeks for patients 1–3 and 13 weeks for patients 4–5). Qi et al reported improvement in mean PTA from 106 ± 9 dB at baseline to 52 ± 30 dB after at least 6 months of follow-up.[12,15] The multinational DB-OTO trial reported that 9 of 12 treated participants (75%) met the primary endpoint of a PTA of 70 dB HL or better at 24 weeks, with 3 participants achieving average normal hearing sensitivity.[16]

The magnitude of individual-level variability warrants emphasis. Across published trials, individual outcomes span a range of more than 90 dB, from no measurable improvement to normalized hearing.[17] This heterogeneity is not well explained by available data, and understanding its determinants is a critical open question. A post hoc audiological characterization of 10 patients from the ChiCTR2200063181 cohort reported progressive improvements in ABR wave V latency and amplitude over the first year, consistent with ongoing auditory pathway maturation, and found that patients with prior contralateral cochlear implant experience exhibited more rapid neural responses.[18]

Table 6a. Characteristics of Included Human Gene Therapy Studies — Identification and Design (Grouped by Trial Registration)

Study (Year)	Country	Design	n	Enrolled Age Range
ChiCTR2200063181 (Fudan/Refreshgene program)				
Lv et al (2024)	China	Single-arm	6	1.0–6.2 yr
Wang et al (2024)	China	Single-arm	5	1.2–11.0 yr
Cheng et al (2025)	China	Nonrandomized cohort (GT vs CI)	11 (GT arm)	1.0–10.9 yr
NCT05901480 (Otovia program)				
Qi et al (2024)	China	Case series	2	5 and 8 yr
Qi et al (2025)	China (5 sites)	Single-arm	10	1.5–23.9 yr
NCT05788536 (DB-OTO program, Regeneron/Akouos)				
Valayannopoulos et al (2026)	Multinational	Open-label registrational	12	10 mo–16 yr

Table 6b. Characteristics of Included Human Gene Therapy Studies — Intervention, Outcomes, and Safety

Study (Year)	Gene Target / Vector	Delivery	Key Auditory Outcomes	Safety
ChiCTR2200063181 (Fudan/Refreshgene program)				
Lv et al (2024)	OTOF / dual AAV1-hOTOF	Intracochlear (RW)	ABR improved ~40–57 dB at 26 wk	No DLT; grade 1–2 AEs; 1 grade 3 (neutropenia)
Wang et al (2024)	OTOF / dual AAV1-hOTOF	Bilateral intracochlear	Ear-specific average ABR thresholds improved from >95 dB bilaterally to 50–85 dB at the latest reported assessment (13 or 26 weeks); sound localization was restored.	No serious AEs
Cheng et al (2025)	OTOF / dual AAV1-hOTOF	Intracochlear	ABR ~55 dB; speech-in-noise advantage vs CI	No major safety signal
NCT05901480 (Otovia program)				
Qi et al (2024)	OTOF / dual AAV-OTOF (Anc80L65)	Intracochlear	Near-normal hearing in younger patient	No major safety concerns
Qi et al (2025)	OTOF / dual AAV-OTOF (Anc80L65)	Intracochlear	PTA improved from 106 ± 9 to 52 ± 30 dB	162 grade I/II AEs; no SAEs
NCT05788536 (DB-OTO program, Regeneron/Akouos)				
Valayannopoulos et al (2026)	OTOF / dual AAV1 (DB-OTO)	Intracochlear	9 of 12 (75%) achieved PTA ≤70 dB HL at week 24; 3 achieved average normal hearing sensitivity.	67 AEs; 2 grade 3 SAEs (resolved); no discontinuations

Note for Tables 6a and 6b. Three programs are represented across six publications. Lv, Wang, and Cheng report sequential and partially overlapping cohorts from ChiCTR2200063181; the 11 participants reported in Cheng (gene therapy arm) include the 6 participants of Lv plus the 5 additional participants enrolled after the protocol amendment reported in Wang. Qi 2024 reports the first two participants of the Otovia cohort (NCT05901480) subsequently expanded to ten and reported in Qi 2025. Valayannopoulos 2026 reports the DB-OTO trial (NCT05788536) with 12 participants and no overlap with the other programs. The aggregate unique participant count is approximately 33. ABR = auditory brainstem response; AE = adverse event; CI = cochlear implantation; DLT = dose-limiting toxicity; GT = gene therapy; PTA = pure-tone audiometry; RW = round window; SAE = serious adverse event.

Table 7. Dual-AAV Platform Strategies Used Across Included Studies

Capsid / Platform	Studies Using This Approach	Key Considerations
AAV serotype 1 (AAV1)	Lv et al 2024; Wang et al 2024; Cheng et al 2025; Valayannopoulos et al 2026 (DB-OTO)	Established serotype; DB-OTO uses hair-cell-specific Myo15 promoter
Synthetic Anc80L65	Qi et al 2025	Enhanced cochlear hair cell transduction efficiency reported in preclinical models
AAV-OTOF (capsid not specified)	Qi et al 2024	Dual-vector system confirmed; specific capsid not disclosed in published report

Table 8a. Study-Level Outcome Comparison — Design and Endpoint Definitions

Study	Baseline	Follow-up	Primary Endpoint	Responder Definition
Lv et al (2024)	ABR >95 dB in all 6 participants	26 wk	Dose-limiting toxicity at 6 wk	≥10 dB reduction in average ABR threshold
Wang et al (2024)	ABR >95 dB bilaterally in all 5 participants	13–26 wk	Dose-limiting toxicity at 6 wk	≥10 dB reduction in average ABR threshold
Cheng et al (2025)	Profound baseline; matched comparator cohort with cochlear implantation	12 mo	Auditory and speech outcomes vs CI (nonrandomized cohort)	Not formally defined
Qi et al (2024)	ABR >95 dB and PTA >100 dB (n = 2)	~1–3 mo	Safety/efficacy (case series)	Not formally defined
Qi et al (2025)	PTA 106 ± 9 dB; click ABR 101 ± 1 dB; tone-burst ABR 91 ± 4 dB; ASSR 80 ± 14 dB (n = 10)	6–12 mo	Safety/tolerability within 5 yr (efficacy secondary)	Not formally defined
Valayannopoulos et al (2026)	Severe-to-profound bilateral hearing loss with biallelic OTOF variants	24 wk	Improvement in average PTA at week 24	PTA ≤70 dB

Table 8b. Study-Level Outcome Comparison — Results and Speech Perception Instruments

Study	Magnitude of Change	Speech Perception Measures
Lv et al (2024)	ABR reduced by 40–57 dB at 0.5–4.0 kHz in 5 of 6 participants	MAIS/IT-MAIS, CAP, SIR, MUSS, SSQ-P (descriptive; improved in responders)
Wang et al (2024)	ABR restored to 50–85 dB across participants; ASSR similarly improved; RMSE 92.8° → 40.0° (P1)	MAIS/IT-MAIS, CAP, SIR, MUSS, SSQ-P (improved in all 5)
Cheng et al (2025)	ABR ~55 dB in GT arm; speech-in-noise advantage relative to CI in select domains	Multiple speech batteries with CI comparator
Qi et al (2024)	Near-normal hearing in 5-yr-old (unilateral); marked PTA and speech improvement in 8-yr-old (bilateral)	PTA, speech recognition (descriptive)
Qi et al (2025)	PTA 106 → 52 ± 30 dB; click ABR 101 → 48 ± 26 dB; tone-burst ABR 91 → 57 ± 19 dB; ASSR 80 → 64 ± 21 dB	Heterogeneous speech assessments across 5 sites
Valayannopoulos et al (2026)	9 of 12 participants (75%) achieved PTA ≤70 dB HL at week 24; 3 achieved average normal hearing sensitivity.	Functional auditory outcomes reported descriptively; 6 participants could hear soft speech without assistive devices.

Note for Tables 8a and 8b. Baseline and follow-up values are reported as published. Responder definitions are stated where the original investigators specified one. Within the ChiCTR2200063181 program, the participants in Lv (n = 6), Wang (n = 5), and Cheng (n = 11) overlap; the n = 11 reported by Cheng comprises the combined cohort across the unilateral and bilateral protocol arms. Cross-study comparison is limited by heterogeneity in measurement instruments, definitions, and reporting frameworks. ABR = auditory brainstem response; ASSR = auditory steady-state response; CAP = Categories of Auditory Performance; CI = cochlear implantation; GT = gene therapy; IT-MAIS = Infant–Toddler MAIS; MAIS = Meaningful Auditory Integration Scale; MUSS = Meaningful Use of Speech Scale; PTA = pure-tone average; RMSE = root mean square error; SIR = Speech Intelligibility Rating; SSQ-P = Speech, Spatial, and Qualities of Hearing Scale for Parents.

3.4. SHORT-TERM SAFETY

Safety reporting across the six publications was uniformly described as favorable, with no dose-limiting toxicity, no treatment-related serious adverse events, and no participants discontinued for adverse events. A more disciplined reading separates this signal into domains that the current evidence can and cannot address.

Surgical delivery risks are inherent to intracochlear administration and overlap substantially with the established risk profile of cochlear implantation, including the use of general anesthesia in very young children and round window or stapes fenestration approaches. In the DB-OTO trial, 17 of 67 reported adverse events were attributed to the surgical delivery procedure, and two grade 3 serious adverse events occurred (mastoiditis in a contralateral implanted ear and walking instability), both of which resolved.[16] The remaining programs did not report procedural complications attributable to the surgical route, although the small total of surgical exposures across all programs limits the statistical resolution of this assessment.

Vector-related and immune risks include responses to the AAV capsid and to transgene-expressing cells. In the three published Chinese trials, a pooled analysis identified 244 grade I/II adverse events and 2 grade III adverse events, with no detectable systemic T-cell activation against the capsid within the reported follow-up.[17] Transient anti-otoferlin antibodies appeared in approximately half of DB-OTO participants and were generally undetectable by week 12.[16] These observations are reassuring within their temporal window but do not address delayed humoral or cellular responses, and the implications for re-administration or contralateral treatment in patients who have already developed neutralizing antibodies are unresolved.

Auditory and vestibular risks include transient threshold shifts, perilymphatic disturbance from injection volume, and potential effects on residual outer hair cell function. Transient reductions in distortion product otoacoustic emission signal-to-noise ratios have been reported in the immediate post-injection period in the Fudan/Refreshgene cohort, with partial recovery during follow-up; these have been attributed to procedural rather than vector-related causes but have not been systematically characterized across programs. Vestibular outcomes were not consistently reported.

Device-related confounding warrants explicit acknowledgment in the subset of participants with concurrent or prior cochlear implantation. Cheng et al directly compared gene therapy against cochlear implantation in a nonrandomized cohort,[13] and the DB-OTO program enrolled at least one participant whose contralateral ear contained a cochlear implant.[16] The presence of implants in the contralateral ear introduces interpretive complications for both auditory outcome measures and safety attribution, particularly for adverse events that could plausibly be attributed to either the implant or to the gene therapy administration.

Long-term safety remains substantively unaddressed. Follow-up durations across the published evidence range from approximately 1 to 12 months, which is insufficient to evaluate outcomes of genuine concern over a patient's lifetime: persistence of viral vector sequences in cochlear tissue, durability of transgene expression, potential for delayed immune responses to viral capsid proteins[19,20] and long-term structural consequences of intracochlear injection in developing auditory and vestibular systems. The absence of early harm is necessary but not sufficient as an indicator of long-term safety, particularly in young pediatric populations exposed to viral vectors during a developmentally sensitive period.

3.5. REGISTRY-DERIVED TRIAL LANDSCAPE

The registry search identified 632 records across ClinicalTrials.gov, ICTRP, ChiCTR, and CTIS prior to screening and deduplication. Following within-source deduplication (358 unique identifiers), topic-based filtering (87 hearing-related records), cross-registry deduplication (removing 18 duplicates), and eligibility screening (applying criteria to 69 provisionally deduplicated records entering screening; three additional cross-registry duplicates were identified during screening), nine unique interventional gene therapy trials were retained (Table 9).

Of the nine trials, eight target OTOF-related deafness, spanning programs registered across the United States, China, and Europe. The remaining trial (ChiCTR2500111936, evaluating EHT201) targets GJB2-associated hearing loss and represents the only currently registered interventional program extending beyond the OTOF biological niche. No interventional trials targeting TMC1 were identified in any registry source.

4. DISCUSSION

The central tension in this field lies between a narrow but coherent published evidence base and a broader, rapidly evolving clinical development landscape that the literature alone does not capture. The six published reports provide early evidence that gene replacement targeting OTOF-related deafness can produce clinically meaningful improvements in auditory function. At the same time, the registry data make clear that the field has already moved beyond the published evidence, with nine registered interventional gene therapy trials identified across multiple regulatory settings and vector platforms, with limited expansion beyond OTOF to additional genetic targets.

Considered on its own, the published record appears narrow and potentially premature as a basis for broad clinical conclusions: small samples (approximately 33 unique participants across three independent clinical programs, with two of those programs contributing sequentially reported overlapping cohorts), short follow-up, single-arm designs, and a single genetic target. Considered alongside the registry data, however, the picture is one of a field in clinical transition, moving from proof-of-concept in a controlled and favorable biological context toward early-stage expansion across multiple programs.

The near-exclusive concentration of both published and registry-derived evidence on OTOF-related deafness de-

Table 9. Final Registry-Derived Trial Dataset[1]

Trial ID	Registry	Therapy	Gene Target	Platform	Status
NCT05788536	ClinicalTrials.gov	DB-OTO	OTOF	Dual AAV1	Recruiting
NCT05821959	ClinicalTrials.gov	AK-OTOF (AAVAnc80-hOTOF)	OTOF	Dual AAV (Anc80L65)	Recruiting
NCT05901480	ClinicalTrials.gov	OTOV101N/C	OTOF	Dual AAV (Anc80L65)	Unknown (last known status: Recruiting)
NCT06370351	ClinicalTrials.gov	SENS-501	OTOF	AAV	Recruiting
NCT06722170	ClinicalTrials.gov	EH002	OTOF	Gene therapy	Recruiting
NCT07288580	ClinicalTrials.gov	EHT102	OTOF	Gene therapy	Recruiting
ChiCTR2200063181	ChiCTR	RRG-003	OTOF	Dual AAV1	Recruiting
ChiCTR2400091517	ChiCTR	EA0010	OTOF	Gene therapy	Not recruiting
ChiCTR2500111936	ChiCTR	EHT201	GJB2	Gene therapy	Recruiting

serves careful analysis. The underlying pathology involves disruption of otoferlin-dependent synaptic vesicle exocytosis at the inner hair cell ribbon synapse, which impairs sound encoding while leaving hair cells intact, afferent neural connections functional, and the broader cochlear architecture undisturbed.[6] Under these conditions, restoring a single missing protein can rescue an otherwise intact system. That context contrasts sharply with the biology of other major hereditary hearing loss subtypes.

GJB2-related deafness, which accounts for a substantial proportion of congenital nonsyndromic hearing loss globally, involves disruption of connexin 26 in cochlear gap junctions, impairing the potassium recycling that sustains the endocochlear potential.[21] This is a system-level metabolic disturbance rather than a localized functional deficit, and the resulting pathology may involve early or progressive structural compromise of the cellular substrate. Only a single interventional gene therapy trial targeting GJB2 was identified (ChiCTR2500111936). Its results will be particularly informative for understanding whether the favorable biology of OTOF can be replicated in a structurally more complex genetic context.

TMC1-related hearing loss presents a different set of constraints. TMC1 encodes a critical component of the mechanotransduction channel in cochlear hair cells[22,23] and gene replacement strategies have shown functional restoration in preclinical models.[3] The challenge is one of timing: in mouse models of TMC1-related deafness, hair cell function is progressively lost over early postnatal development, and the therapeutic window for effective gene replacement appears to be narrow, though the precise translation of this window to human cochlear development has not been conclusively established. The absence of any registered interventional TMC1 trials is consistent with these constraints.

The biological explanations advanced above are plausible and consistent with available preclinical and clinical evidence, but they should be marked as interpretive rather than established. Target underrepresentation in the trial landscape may also reflect non-biological factors, including commercial strategy, intellectual property considerations, vector design constraints, regulatory risk tolerance, and the practical feasibility of trial enrollment for ultra-rare genetic subtypes. Biological tractability is a necessary but not sufficient explanation for the observed asymmetry, and the absence of TMC1 trials in particular may be attributable in part to factors not visible from the registry data alone.

The rapid expansion of the OTOF clinical pipeline introduces its own interpretive challenges. With multiple independent programs advancing under different regulatory frameworks and testing related but distinct therapeutic products, the risk of generating a fragmented dataset is substantial. The current evidence base includes ABR thresholds, pure-tone averages, speech perception assessments conducted with varying instruments, and sound localization measures, none of which have been harmonized into a common reporting framework. Without such consensus, cross-trial comparison will remain limited even as the number of trials grows.

The field's trajectory is one of a transition that is well underway but far from complete. What the field now needs is methodological consolidation: agreement on outcome

1 Note. Recruitment statuses reflect registry entries as captured on April 17, 2026, the date of the registry search. ClinicalTrials.gov classified NCT05901480 as Unknown because its last known Recruiting status, last verified in August 2023, had not been verified within the preceding two years. Subsequent regulatory developments are described in the Note Added in Revision.

standards, longer follow-up in existing trials, systematic expansion beyond OTOF into biologically tractable alternative targets, and a rigorous framework for evaluating the relationship between timing of intervention and therapeutic outcome.[24]

5. LIMITATIONS

Several limitations of this review should be acknowledged. The published evidence base is restricted to a small number of early-phase studies originating from three independent clinical programs, with overlapping cohorts across sequential reports within two of those programs, limited sample sizes, and short follow-up durations, all of which constrain the robustness and generalizability of conclusions. The bibliographic search was limited to a single database (PubMed), which may have resulted in the omission of studies indexed exclusively in EMBASE, Cochrane CENTRAL, Scopus, Web of Science, or regional databases. This limitation was partially mitigated by systematic registry searches across four platforms, but the review is appropriately framed as a PubMed-based scoping review rather than as a comprehensive multi-database evidence synthesis. Title and abstract screening was conducted by a single primary reviewer, with independent verification by a second reviewer at the full-text and registry stages. While inter-reviewer agreement was high and disagreements were resolved without third-reviewer adjudication, the absence of dual independent screening from the initial title-and-abstract stage represents a residual methodological limitation. Grey literature, including conference proceedings, preprints, and industry communications, was not systematically searched. This decision was made to maintain a clear evidentiary distinction between peer-reviewed and formally registered evidence, but it may result in the omission of recent data not yet available through either of those channels. This constraint is most consequential for the DB-OTO program, for which longer follow-up data have been disclosed through conference presentations and sponsor communications but not yet incorporated into the peer-reviewed record captured by the present search; this constraint also bears on regulatory developments postdating the search window. Registry-derived data were incorporated as a complementary source, but registry entries vary in completeness, are subject to retrospective amendment, and reflect stated intentions rather than published findings. Heterogeneity in outcome measurement across studies precluded quantitative synthesis and limits the interpretive precision of the narrative analysis. No protocol for this scoping review was prospectively registered, which is noted in the interest of transparency and acknowledged as a deviation from PRISMA-ScR best practice.

6. CONCLUSION

Gene therapy for hereditary hearing loss has produced early human data consistent with meaningful auditory improvement within a single, biologically favorable genetic subtype, though the evidence remains limited in size, follow-up duration, and genetic scope. The six published human studies demonstrate what has been shown rather than what has been established: a reproducible directional signal in OTOF-related deafness, generated across three independent clinical programs treating approximately 33 unique participants in total, using closely related dual-AAV platforms, with participant-level overlap across several publications within two of those programs. Registry data document continued expansion of clinical development, with nine registered interventional gene therapy trials across multiple regulatory settings, though registry activity reflects institutional commitment rather than confirmed therapeutic benefit. The concentration of both published and registered evidence on OTOF reflects translational constraints that the available data do not resolve, with biological tractability a necessary but not sufficient explanation. Long-term safety, durability of transgene expression, determinants of individual variability in response, and translatability to other genetic subtypes remain open questions that published short-term outcomes cannot answer. Establishing whether early improvements persist, whether they generalize beyond OTOF, and whether the current platform designs are the right ones for structurally more complex forms of hereditary hearing loss will depend on longer follow-up in existing cohorts, completion of trials targeting alternative genes such as GJB2, and the emergence of independently replicated data across regulatory jurisdictions. The present evidence base supports continued investigation; it does not yet support broader clinical conclusions.

NOTE ADDED IN REVISION

Searches reported in this review closed on April 17, 2026, prior to subsequent regulatory developments. On April 23, 2026, the U.S. Food and Drug Administration granted accelerated approval to Otarmeni[25] (lunsotogene parvec-cwha), the dual-AAV gene therapy formerly designated DB-OTO and corresponding to the Valayannopoulos et al (2026) report included in this review (NCT05788536), for pediatric and adult patients with severe-to-profound and profound sensorineural hearing loss associated with molecularly confirmed biallelic variants in the OTOF gene, preserved outer hair cell function, and no prior cochlear implant in the same ear. This represents the first regulatory approval of an inner-ear gene therapy for a hereditary hearing loss subtype. The substantive findings of the present review, including the concentration of human evidence within OTOF-related deafness, the overlap of cohorts across sequential publications within individual clinical programs, the short follow-up of available data, and the narrow target representation across the registry landscape, remain unchanged by this development. The framing of the field as wholly pre-approval no longer applies for the OTOF subtype, although the broader landscape of hereditary hearing loss remains without a disease-modifying therapy.

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CONFLICT OF INTEREST / COMPETING INTERESTS

The authors declare no conflicts of interest relevant to this work.

ETHICS APPROVAL AND CONSENT

This study was a scoping review of publicly available published literature and clinical trial registry records. It did not involve the recruitment of human participants, the collection of identifiable personal data, or any new intervention involving humans or animals. Therefore, institutional ethics approval and informed consent were not required.

AI TOOL USE DISCLOSURE

Generative artificial intelligence tools were used to assist with language editing. The authors reviewed, verified, and revised all AI-assisted content and take full responsibility for the accuracy, integrity, interpretation, and final presentation of the work. Artificial intelligence tools were not used to determine study eligibility, extract data, analyze findings, or make final methodological or interpretive decisions.

THIRD-PARTY MATERIAL PERMISSIONS

All tables and figures were created specifically for this manuscript. No third-party copyrighted material requiring permission has been reproduced or adapted.

DATA AVAILABILITY

All data analyzed in this review were obtained from publicly available published articles and clinical trial registry records. The data supporting the findings are presented within the manuscript and its supplementary materials. The complete registry screening and eligibility audit trail is provided in Supplementary Table S1. No additional participant-level dataset was generated.

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REPORTING GUIDELINES

This scoping review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR).

PREPRINT DISCLOSURE

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Supplementary Table S1. Complete Registry Search Query Log[1]

Source	Query String	Date Run	Records Returned
ClinicalTrials.gov	hearing loss gene therapy	April 17, 2026	77
ClinicalTrials.gov	deafness gene therapy	April 17, 2026	74
ClinicalTrials.gov	cochlea gene therapy	April 17, 2026	17
ClinicalTrials.gov	inner ear gene therapy	April 17, 2026	24
ClinicalTrials.gov	sensorineural hearing loss gene	April 17, 2026	39
ClinicalTrials.gov	cochlear gene therapy	April 17, 2026	17
ClinicalTrials.gov	OTOF	April 17, 2026	13
ClinicalTrials.gov	otoferlin	April 17, 2026	12
ClinicalTrials.gov	DFNB9	April 17, 2026	14
ClinicalTrials.gov	GJB2	April 17, 2026	6
ClinicalTrials.gov	connexin 26	April 17, 2026	4
ClinicalTrials.gov	DFNB1	April 17, 2026	5
ClinicalTrials.gov	TMC1	April 17, 2026	0
ClinicalTrials.gov	AAV hearing	April 17, 2026	5
ClinicalTrials.gov	AAV deafness	April 17, 2026	4
ClinicalTrials.gov	AAVAnc80	April 17, 2026	4
ClinicalTrials.gov	gene transfer hearing	April 17, 2026	27
ClinicalTrials.gov	gene replacement deafness	April 17, 2026	4
ICTRP	hearing loss gene therapy	April 17, 2026	9
ICTRP	deafness gene therapy	April 17, 2026	12
ICTRP	cochlea gene therapy	April 17, 2026	1
ICTRP	inner ear gene therapy	April 17, 2026	11
ICTRP	sensorineural hearing loss gene	April 17, 2026	3
ICTRP	OTOF	April 17, 2026	8
ICTRP	otoferlin	April 17, 2026	1
ICTRP	DFNB9	April 17, 2026	1
ICTRP	GJB2	April 17, 2026	10
ICTRP	connexin 26	April 17, 2026	14
ICTRP	TMC1	April 17, 2026	0
ICTRP	AAV	April 17, 2026	211
ICTRP	AAV hearing	April 17, 2026	11
ICTRP	gene transfer hearing	April 17, 2026	See combined
ICTRP	gene replacement deafness	April 17, 2026	See combined
ChiCTR (direct)	OTOF	April 17, 2026	Captured via ICTRP
ChiCTR (direct)	GJB2	April 17, 2026	Captured via ICTRP
ChiCTR (direct)	TMC1	April 17, 2026	0
ChiCTR (direct)	otoferlin	April 17, 2026	Captured via ICTRP
ChiCTR (direct)	deafness gene therapy (English + Chinese)	April 17, 2026	Captured via ICTRP
CTIS (direct)	OTOF	April 17, 2026	3
CTIS (direct)	otoferlin	April 17, 2026	3
CTIS (direct)	GJB2	April 17, 2026	0
CTIS (direct)	gene therapy hearing	April 17, 2026	0
CTIS (direct)	deafness gene therapy	April 17, 2026	0

All searches were conducted on April 17, 2026. TMC1-directed searches returned no results in any registry source. Within-source deduplication yielded 120 unique ClinicalTrials.gov records, 235 unique ICTRP records, and 3 unique CTIS records.
Abbreviations: CTIS, Clinical Trials Information System; ICTRP, International Clinical Trials Registry Platform; ChiCTR, Chinese Clinical Trial Registry.

1 Individual query counts in this table reflect raw export sizes prior to within-source deduplication. Where queries overlapped (e.g., trials returned by both the broad “AAV” query and gene-specific queries such as “OTOF” or “DFNB9”), within-source preliminary deduplication was applied before downstream processing. The ICTRP figure used in Table 4 (n = 280) reflects this preliminary deduplication; the unique trial identifier count (n = 235) reflects full within-source deduplication.