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REVIEW

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Efficiency of gene therapy for sensorineural hearing loss in mouse model: A meta-analysis

Nevra Keskin Yilmaz DVM, PhD[1,2] | Dogukan Ozen DVM, PhD[3] | Rafael da Costa Monsanto MD, PhD[2] | Emre Ocak MD, MSc[4] | Artur Koerig Schuster MD[5] | Tomotaka Shimura MD[2,6] | Sebahattin Cureoglu MD[2]

[1]Department of Internal Medicine, Faculty of Veterinary Medicine, Ankara University, Ankara, Turkey

[2]Department of Otolaryngology Head & Neck Surgery, University of Minnesota, Minneapolis, Minnesota, USA

[3]Department of Biostatistics, Faculty of Veterinary Medicine, Ankara University, Ankara, Turkey

[4]Department of Otolaryngology Head & Neck Surgery, Faculty of Medicine, Ankara University, Ankara, Turkey

[5]Postgraduate Program in Medicine: Surgical Sciences, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil

[6]Department of Otorhinolaryngology, Showa University Fujigaoka Hospital, Yokohama, Japan

Correspondence
Nevra Keskin Yilmaz, University of Minnesota Medical School Otopathology Laboratory, Lion's Research Building, 2001 6th St SE, Minneapolis, MN, 55455, USA.
Email: keskinnevra@gmail.com

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Abstract

Objectives: Sensorineural hearing loss (SNHL) is a disorder characterized by the loss or impairment of cochlear hair cells or the auditory nerve. In recent years, gene therapy has emerged as a promising approach for SNHL treatment. The objective of this study is to evaluate the impact of gene therapy on the restoration or improvement of auditory function in mouse model with loss or impairment of hearing.

Methods: Studies with clear experimental designs, and auditory brainstem response (ABR) analysis as relevant outcome measures were included by searching PubMed, Scopus, and Web of Science databases. The PRISMA guideline was used for abstracting data and assessing data quality and validity. A quantitative synthesis was performed using a random effects model to examine the effect of gene therapy on auditory function in SNHL.

Results: Nine articles including 71 studies meeting the inclusion criteria were identified. These studies explored therapies targeting the TMC1, VGLUT3, USH1C, CLRN1, WHRN, and PJVK genes, with genetic material ranging from 1.8×10^{11} and 1.4×10^{14} gc/mL being delivered to the inner ear through round window membrane, cochleostomy, or posterior semicircular canal injection methods. The hearing test results showed a significant mean difference of 26.91 dB (95% CI: 22.01–31.85) in favor of the experimental group.

Conclusions: Although promising results have been obtained regarding the potential success of gene therapy in SNHL, further investigation is needed to explore the long-term effects of gene therapy, treatment response rates, and the relationships between different genetic mutation types.

KEYWORDS
gene therapy, meta-analysis, mice, sensorineural hearing loss

1 | INTRODUCTION

Hearing is an essential aspect of human interaction with the environment. According to the World Health Organization (WHO), more than 5% of the world's population (~430 million people) experience hearing loss, and it is estimated that over 700 million people will face hearing loss by 2050.[1] The cellular components of the ear that provide hearing and balance are susceptible to genetic and environmental factors that may impact both the overall structure and the function of the ear.[2,3]

Sensorineural hearing loss (SNHL) affects one out of every 1000 newborn babies[4] and has lifelong consequences such as language and communication impairment, leading to social and cultural isolation.[2] Although significant successes have been achieved in the rehabilitation of hearing (such as cochlear implants), there is a rising need for the development of regenerative treatments with the aim of providing "normal" hearing.[5,6] Recently, numerous studies have focused on advancing regenerative medicine approaches to treat hearing loss and many of these investigations, primarily involving animal experiments, emphasize exploring novel treatment strategies based on gene therapy. Studies indicate that delivering molecular agents to the inner ear holds promise in halting or even reversing the progression of hearing loss.[2]

Therapeutic strategies for restoring hearing and balance in mouse models of inner ear disease aim to restore sensory function through gene replacement, augmentation, *knockdown*, or *knockout*. Studies have predominantly focused on using viruses to transfer wild-type genes to the inner ear within the context of regenerative medicine applications in mouse models.[7] The effectiveness of gene therapy for inner ear disorders depends on the choice of vectors, and adenovirus (AdV) and adeno-associated virus (AAV) vectors are particularly favored due to their minimal side effects, high titer preparation, and the ability to transduce quiescent cochlear cells, making them a promising tool for gene transfer.[8,9]

Despite the rapid progress in the field of gene therapies and regenerative medicine, a comprehensive systematic synthesis of preclinical studies evaluating the effectiveness of these applications on hearing function is lacking. Therefore, the objective of this study is to systematically review the available preclinical literature using gene therapy for the treatment of SNHL and measure and statistically analyze the impact of gene therapy on hearing based on auditory brainstem response (ABR) analysis results.

2 | METHODS

We conducted a meta-analysis study to evaluate gene therapy applications for SNHL. For the literature search and study selection, we used the methods proposed by the reporting system "Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020."[10] The review question was formulated according to the acronym PICOTS (population, intervention, comparison, outcomes, time frame, and setting): What is the efficacy of gene therapy on hearing, compared to Control group (no hearing) in SNHL animals?

2.1 | Search strategy

A comprehensive search of Medline was performed on PubMed, Scopus, and Web of Science databases between January 2012 and June 2023. The search strategy used combinations of words and keywords in English, including "gene therapy," "sensorineural hearing loss," "preclinical," "viral vector," "mouse," and their synonyms. The references obtained from the searches were organized in Zotero Reference Manager and Microsoft Excel.

2.2 | Study selection

Duplicates were removed using Zotero Reference Manager. Initially, two blinded and independent authors selected the articles by title and abstract, applying the eligibility criteria according to the abovementioned PICOTS-guided (population, intervention, control, outcomes, time frame, and study design) questions. Subsequently, full texts of the selected studies were retrieved and independently assessed for eligibility by two reviewers (NKY, RM). Any discrepancies were resolved through discussion and an independent expert.

2.3 | Inclusion and exclusion criteria

In this study, data were included based on five main criteria: related disease (SNHL), neonatal mouse as animal model, AdV or AAV as vector, gene replacement as the therapy method, and analysis of hearing function with ABR in the control and experimental groups to evaluate the therapeutic efficacy of gene therapy. "Gene therapy" was defined according to FDA.[11] All studies were chosen to include mice with experimentally induced or hereditary SNHL, had mice treated with gene therapy in the study group, and included a preclinical comparison (control) group that did not receive gene therapy. The review included the strain and genetic modification characteristics of the mouse model (if any), its gender, the number of animals in the study, and the age of the animals.

The following inclusion criteria was applied: (i) original research article, published in a peer-reviewed journal, (ii) publication range spanning between January 2012 and June 2023, (iii) published in English, (iv) studies including neonatal mouse as an animal model, (v) AdV or AAV must be used as the viral vector, (vi) gene replacement must be utilized as the therapy method, (vii) the study must have a control group, (viii) ABR were used for hearing analysis, (ix) detailed information on the transfer methods and their applications must be included.

Exclusion criteria was defined as: (i) not an original article, (ii) irrelevance of the study or existence of secondary diseases, (iii) use of different animal models/age groups, (iv) absence of a control group and/or not specifying the number of animals in the group, (v) the number of mice in the study group is not specified, (vi) therapy method includes a different technique, and (vii) no or insufficient hearing data provided.

2.4 | Data extraction and processing

Data from the articles (text and figures) were extracted independently by two authors and populated in a spreadsheet. If only graphs were available, the data were extracted using a digital screen ruler.

The collected data encompass the characteristics of the study design (number of animals in the control and experimental groups, methods of generating SNHL), animal characteristics, and interventional characteristics (relevant gene, route of administration, dose, delivery method, and timing). The mean values (means) and measures of variation (SDs) of the parameters for the treatment and control groups were extracted. In studies where the standard deviation was not reported, the necessary conversions were made using the formula [SE = SD/√(sample size)].[12] If any location or dispersion measurement was not provided in the studies or if doubts arose, the author of the study was then contacted to obtain necessary information. In studies whose standard deviation data were shown as "0" in the data, the value was taken as "1" in order to calculate the effect size and the analysis was performed.

2.5 | Meta-analysis/statistical analysis

The meta-analysis was performed using Stata v.18 software (StataCorp LP, College Station, TX), with the level of significance set at $p < .05$. Absolute effect/raw difference were calculated and presented, since all the variables were presented in the same units across all studies as recommended by Takeshima et al.[13] A random effect meta-analysis using DerSimonian and Laird[14] estimator with Kapp-Hartung Adjustment was implemented. Cochran's Q test and I^2 test statistic were used to assess heterogeneity. An I^2 value indicates the percentage of variation between studies. The inconsistency was classified according to the following scale: low (<25%), moderate (25–75%), and high (>75%).[15] We used a random effects meta-regression analysis to assess the heterogeneity of effect between studies with one or more characteristics such as gene, frequency, and timing relative to injury.

A forest plot was used in the visual presentation of the findings. Begg test, and Funnel plots were used to assess potential publication bias. Trim and fill method was used to provide a summary effect adjusted for publication bias.[16] A Leave-one-out meta-analysis also performed to investigate the influence of each study on the overall effect size estimate and to identify any potential influential studies.

3 | RESULTS

3.1 | Study selection and characteristics

The systematic review of the literature yielded 9 articles[9,17–25] and 71 comparisons that met the study criteria (Figure 1). See Table 1 for the list of the first authors, publication years and journals and Table 2 for PICOTS descriptions.

The genes treated in the articles evaluated within the study included TMC1, VGLUT, USH1C, CLRN1, PJVK, and WHRN. The age at intervention was limited as P0-P2. Data on the preferred route for the transmission of genetic material to the inner ear were also collected. Genetic material was transferred via the round window membrane (RWM) in seven articles, and the posterior semicircular canal in one article. In one article, both RWM and cochleostomy techniques were used. The dose of the transmitted genetic material ranged between 1.8×10^{11} and 1.4×10^{14} gc/mL. Following the delivery of genetic material, the hearing tests (ABRs) were conducted at varying intervals of 2–24 weeks and at the frequencies of 8, 16, 24, and 32 kHz (Table S1).

3.2 | Main outcomes

The mean estimated difference based on the random effects model was −26.91 dB (95% CI: −31.85 to −22.01) in favor of the experimental group, and this efficiency was statistically significant ($z = -7.85$, $p < .001$) (Figure 2). The I^2 from the test statistics on heterogeneity was 89% ($Q(70) = 665.59$, $p < .001$); which means that 89% of the variability in the effect-size estimates was because of the between-study differences rather than the sampling variation. The between-study variance τ^2 is estimated to be 3.47. A sensitivity analysis with 10% I^2 and $0.25\tau^2$ was also performed to explore various levels of heterogeneity between studies. In both cases, the overall results were still significant in favor of the treatment.

To explore how treatment effect varies across different subgroups of trials and to explain the between function of moderators, a sub-group and meta regression analysis were also performed (Figure 3). Based on the obtained characteristic variables, the overall estimates for each subgroup were significantly in favor of the experimental group. Also, the test for group-specific overall differences in gene ($Q(5) = 77.87$, $p < .001$) and frequency ($Q(3) = 14.46$, $p < .001$) were statistically significant, except timing ($Q(1) = 0.75$, $p = .39$). In terms of heterogeneity, the reported I^2_{res} statistic in the meta regression was still 89.11%, indicating high heterogeneity, using the categorization of Higgins et al.,[15] even after including gene, frequency, and timing relative to injury as the moderators. In other words, 89.11% of the variability in the residuals was still attributed to the between-study variation, whereas only 10.89% was attributed to the within-study variation. The adjusted R^2 statistic indicated that approximately 29% of the variance between studies can be explained by the gene, frequency, and timing relative to injury.

3.3 | Assessment of small study effect and publication bias

Funnel plot (Figure 4) and test statistics were used to examine possible publication bias and small study effect in studies. The average differences were almost symmetrically distributed, yet, with a possibility of several smaller studies missing. However, the results of the

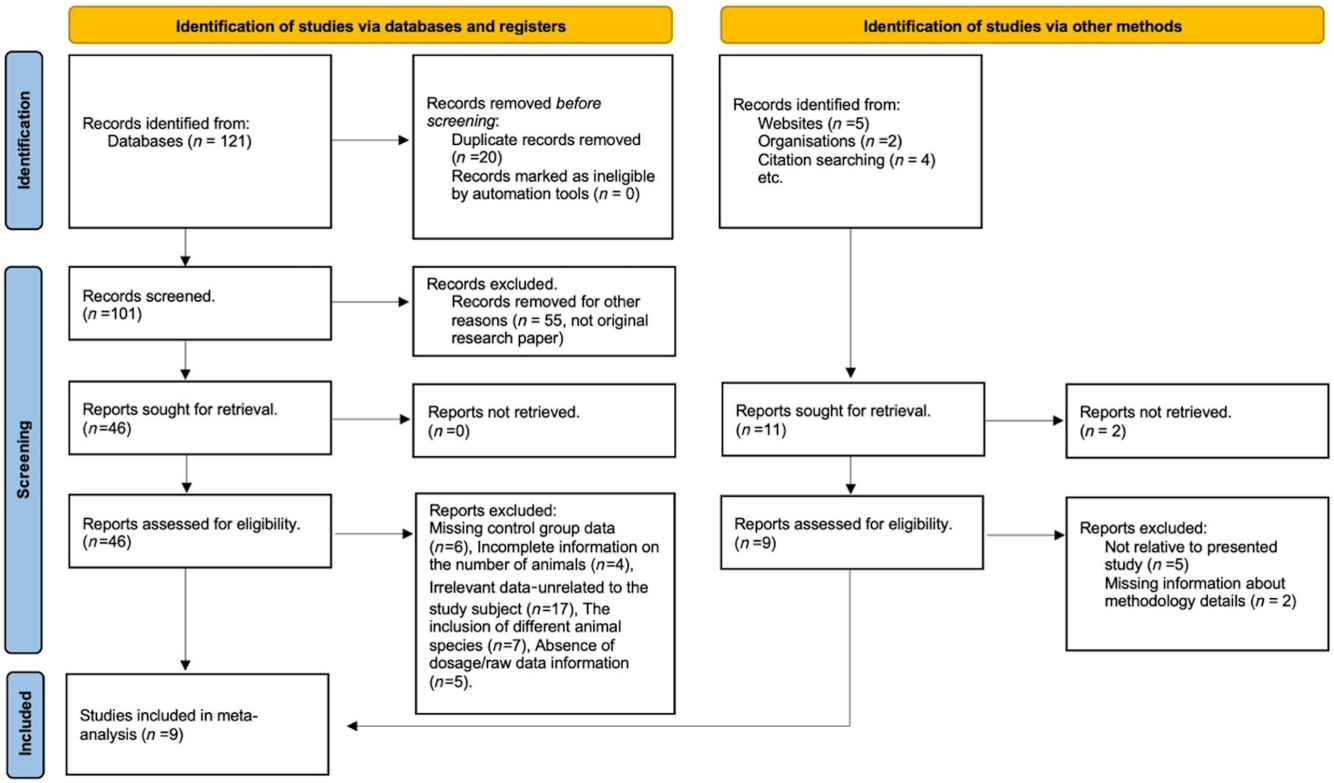

FIGURE 1 PRISMA 2020 flow diagram of demonstrating study selection process (adapted from Page et al.[10]).

TABLE 1 The publications included in the meta-analysis.

First author	Publication year	Journal
Akil[17]	2012	Neuron
Askew[18]	2015	Science Translational Medicine
Pan[19]	2017	Nature Biotechnology
Geng[20]	2017	Scientific Reports
Dulon[21]	2018	Journal of Clinical Investigation
György[22]	2018	Molecular Therapy – Methods & Clinical Development
Nist-Lund[23]	2019	Nature Communications
Lu[9]	2022	Journal of Clinical Investigation Insight
Isgrig[24,25]	2017 (2022)[a]	Molecular Therapy

[a]Published erratum.

TABLE 2 *PICOTS* descriptions.

Population	Neonatal mice animal model
Intervention	Gene therapy
Comparison	Auditory Brainstem Response analysis of mice with hearing loss and those treated with gene therapy
Outcomes	Quantitative measurement of hearing function, analysis regarding the related gene, test frequency, timing relative to injury
Time frame	Available literature between January 2012 and June 2023
Setting	Pre-clinical study

regression-based Egger tests ($t = -1.56$, $p = .124$) and the nonparametric Begg's test for small-study effect ($z = -1.43$; $p = .155$) did not provide evidence of a small study effect. This suggests that the small visual deviation from symmetry is possibly caused by the presence of between-study heterogeneity. In support of the findings, the trim-and-fill analysis to overcome the effect of any possible bias showed no change in the overall effect (−28.17 kHz vs. −26.93 kHz) (Figure S1).

A leave-one-out sensitivity analysis was conducted to examine the individual effects of the studies included in the meta-analysis on the results (Figure S2). No study was found to have a direct major effect on the combined mean difference.

4 | DISCUSSION

SNHL is a prevalent condition that affects both humans and animals, characterized by damage to the cochlear hair cells or the neural pathway responsible for transmitting auditory information to the brain. As a multifactorial disease, understanding the causes and consequences of SNHL is crucial for preventing and treating sensory disorders that substantially impact the quality of life for individuals.[26]

ABR, used for the hearing analysis, reflects the electrical responses of the cochlea and neural functions in the auditory

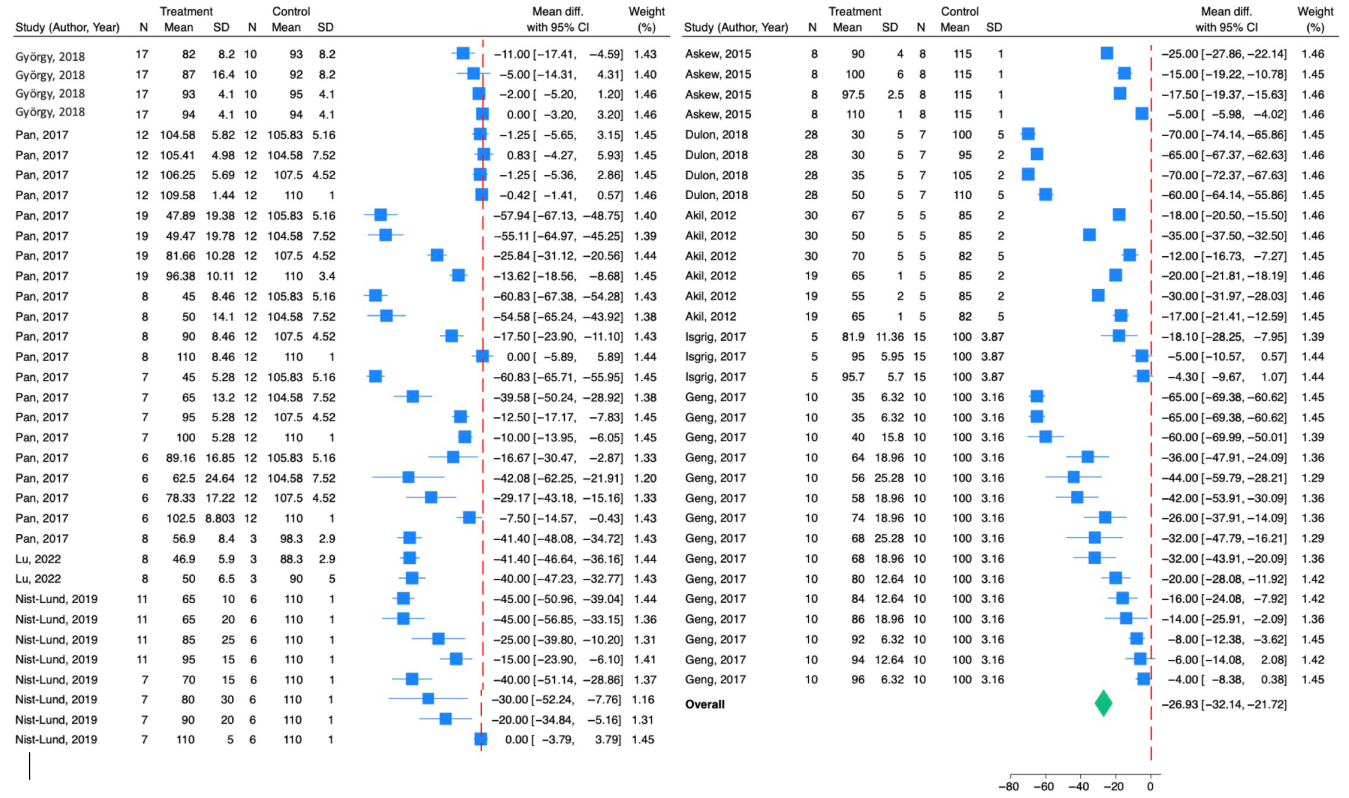

FIGURE 2 Forest plot of the studies for the overall impact in the included studies.

pathway. The collected data showed an improvement of 26.91 dB in ABR measurements in favor of the experimental group. In a meta-analysis exploring the effectiveness of mesenchymal stem cells in SNHL, this difference was determined as 15.22 dB.[27] Consistent with the present meta-analysis findings, numerous studies conducted to date highlight the efficacy of regenerative medicine treatments in mouse models for preventing or treating various causes of hearing impairment. Consequently, regenerative medicine applications emerge as promising approaches to prevent or treat genetic causes of hearing disorders.[7,27–29]

While individual studies within a specific research area often report similar results, differences arise when these studies are included in a meta-analysis.[30] The significant and high heterogeneity identified among the studies included in the present report is a limitation. The heterogeneity likely stems from the diverse methodological design of the studies. Heterogeneity poses challenges in combining meta-analysis results. However, although heterogeneity is expected in an emerging field such as gene therapy, we emphasize the importance of adopting a common methodological approach to enhance comparability of results in gene therapy research.

As this study is based on published data on gene therapy, the results should be interpreted considering the potential effects of publication bias. Therefore, Trim-Fill analysis was performed to demonstrate how the effects of publication bias might change with the addition of more publications if possible.[31,32] The Trim-Fill analysis showed that the difference observed in favor of the experimental group, although reduced, persists. This also supports the perspective that the potential effectiveness of gene therapy remains under the assumption of filling in missing data using predictive results.

Following the heterogeneity identified in the study, subgroup analyses were conducted. According to the meta-analysis data, it was observed that the effectiveness of gene therapy decreased as the frequency increased. This finding suggests that the frequency distribution of hearing loss may impact the effectiveness of treatment. Gene therapy may be more effective in specific frequency regions of hearing loss, while its effectiveness may be limited to the lower frequencies.

High-frequency SNHL can arise from many pathologies, including ototoxic drug use, genetic diseases, acoustic trauma, and labyrinthitis. In a human temporal bone study focusing on cases of suppurative labyrinthitis, Kaya et al.[33] reported that the degeneration of cochlear hair cells and spiral ganglion cells was most intense in the cochlear basal fold, with the percentage of cells that degenerated towards the apex decreasing. Similarly, another otopathology study examining cochleosaccular dysplasia in dogs reported that degenerative findings were more pronounced at the cochlear base.[34] These studies highlight that hair cell sensitivity to injury is heightened at the cochlear base.

According to the tonotopic mapping of the cochlea, the basal turn performs the analysis of high frequencies while the apex analysis the low frequencies. Previous studies show that regenerative medicine applications have limited success at high frequency. Considering that in most diseases hair cell death starts from the basal and moves

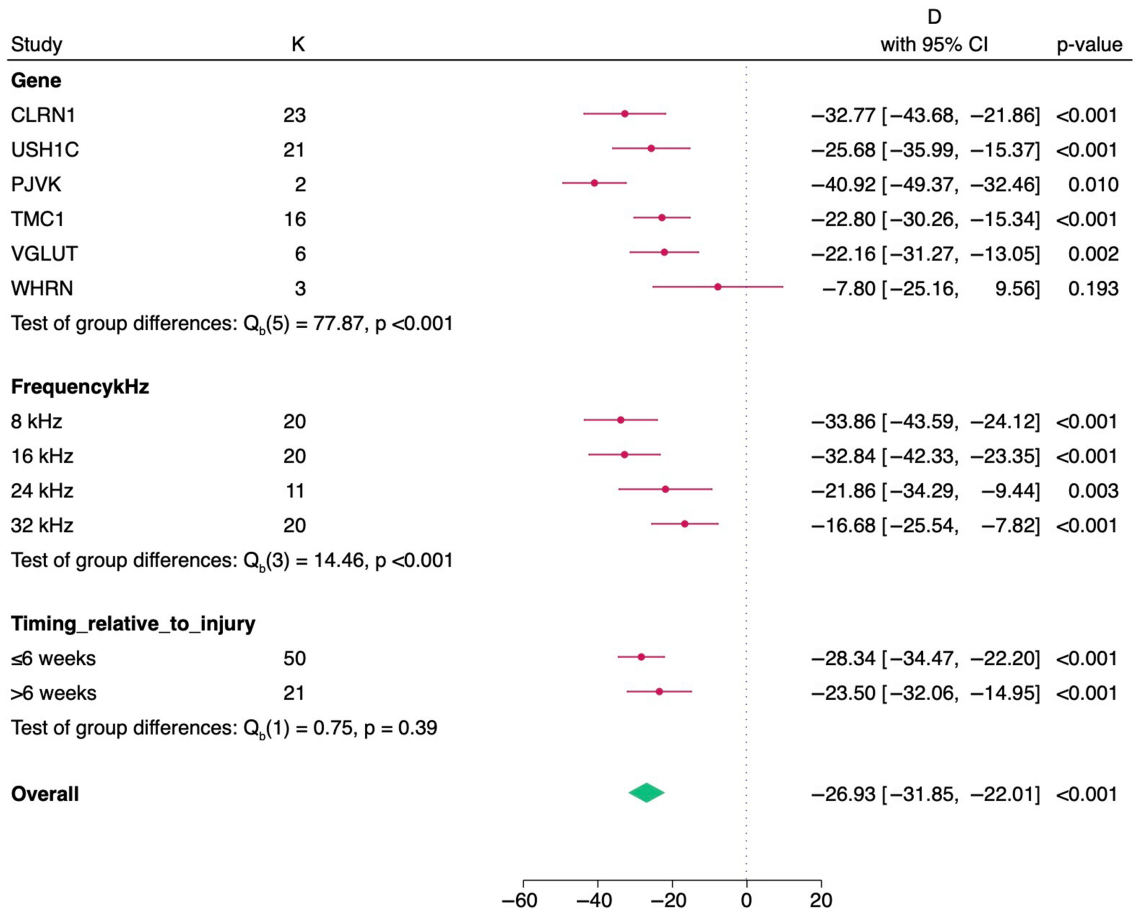

FIGURE 3 Forest plot for subgroup analysis of the included studies.

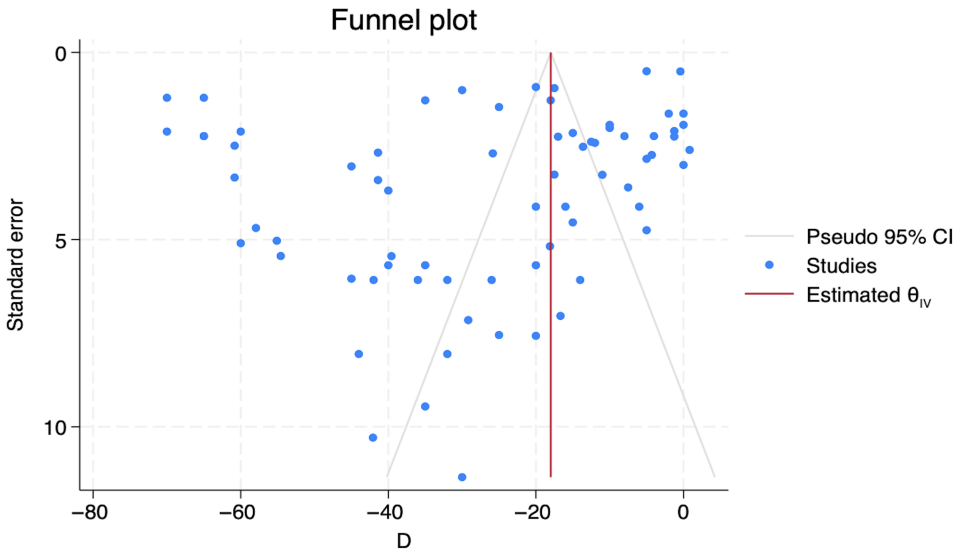

FIGURE 4 Funnel plot analysis indicating absence of small study effect.

towards the apex, and outer hair cells degenerate faster than inner hair cells, it should be considered that basal turn regeneration required for high frequency hearing depends on many factors. Among these factors, there are many structural and cellular elements such as spiral ligament, stria vascularis, support cells and microenvironment, and therefore the treatment should be planned considering all these factors.[23,35,36]

Only mice aged P0-P2 were included in this meta-analysis, a factor that may contribute to the success of gene delivery. The microinjection of bioactive substances into the early neonatal mouse inner

ear has led to recent advancements in the field of inner ear gene therapy. The plasticity observed in the early neonatal mouse inner ear is likely attributed to its functional immaturity, as hearing only begins to emerge at the end of the second postnatal week. Studies, aligning with the meta-analysis results, have demonstrated that the therapeutic interventions conducted during the early neonatal therapeutic efficacy window exhibit a high effect. This suggests that therapeutic benefits diminish or are lost after this period. The finding that the greatest impact on the success of post-injection hearing analysis, as revealed in subgroup analysis, is achieved in the first weeks is also consistent with these data.[37–39]

Meta-regression analysis is a method employed to explore the relationship between intervention effects and one or more variables. Upon evaluating meta-regression data in this meta-analysis study, heterogeneity is observed between the studies, which could be attributed to differences in study designs. Heterogeneity could arise from variations in study designs, encompassing differences in randomization methods, blinding procedures (if any), confounding control strategies, and the experimental unit to which the treatment was randomized. Another finding is the identification of variables that significantly differ from reference values. Considering these factors, it can be inferred that different combinations may exert varying levels of influence on the effectiveness of gene therapy.[32] Therefore, reasonable to expect variations in the overall effect depending on the study.

5 | CONCLUSIONS

SNHL arises from the degeneration of the sensory cells of the inner ear and the acoustic nerve. The prospect of gene therapy has emerged as a potential therapeutic avenue for SNHL, providing an opportunity to directly address the genetic factors contributing to hearing impairment. Animal models have been instrumental in shedding light on the effectiveness and safety of gene therapy interventions. This meta-analysis study reveals improvements in hearing loss attributable to the administration of therapeutic genes in mouse models of SNHL.

Gene therapy offers a significant advantage in the realm of personalized treatment. Tailoring interventions based on the specific genetic mutation responsible for SNHL allows for diverse strategies. Personalized gene therapy interventions may involve utilizing specific viral vectors with enhanced transduction rates in target inner ear cells, optimizing promoter selection for precise gene expression, and effectively addressing or compensating for the genetic defect. Animal models serve as invaluable tools to understand the safety profile of gene therapy interventions in the inner ear. Hence, sustaining preclinical studies and transitioning regenerative medicine applications to the clinical phase is of paramount importance.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ORCID

Nevra Keskin Yilmaz https://orcid.org/0000-0002-6287-1157
Dogukan Ozen https://orcid.org/0000-0003-1943-2690
Rafael da Costa Monsanto https://orcid.org/0000-0002-9124-593X
Emre Ocak https://orcid.org/0000-0003-0652-2777
Artur Koerig Schuster https://orcid.org/0000-0002-1431-3855
Tomotaka Shimura https://orcid.org/0000-0003-1164-6977
Sebahattin Cureoglu https://orcid.org/0000-0001-9220-7073

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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