Original Article

DOI: 10.5582/irdr.2024.01072

Research hotspots and trends of the *SLC26A4* gene-related hearing loss from the perspective of knowledge graph

Yue Li[1,2,3], Cheng Wen[1,2,3], Yiding Yu[1,2,3], Lin Deng[1,2,3], Shan Gao[1,2,3], Lihui Huang[1,2,3,*]

[1] Department of Otolaryngology-Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University, Beijing, China;
[2] Beijing Institute of Otolaryngology, Beijing, China;
[3] Key Laboratory of Otolaryngology-Head and Neck Surgery (Capital Medical University), Ministry of Education, Beijing, China.

SUMMARY: This article aims to identify research hotspots and trends in research on *SLC26A4* gene-related hearing loss through bibliometric and visual analyses, providing a reference and direction for future research. Publications on *SLC26A4* gene research in hearing loss from 1994 to 2023 were retrieved from the Web of Science Core Collection database. Bibliometric analysis was conducted using the Bibliometrix 4.0.0 R package, CiteSpace 6.2.R6 software, and VOSviewer 1.6.20. The analysis encompassed journals, authors, keywords, institutions, countries, and references. Based on the analysis results, network maps were generated to evaluate collaborations among authors, countries, institutions, keyword co-occurrences, and co-citation references. This study identified 1,308 publications from 62 countries. Annual publication numbers have increased with fluctuations, showing rapid growth since 2011. The USA emerged as the leading contributor in this field based on scientific production, citations, and cooperation networks. *International Journal of Pediatric Otorhinolaryngology* had the highest number of publications, while *Laryngoscope* was the most cited journal. Harvard University was the most productive institution. Key researchers included Dai Pu, Griffith Andrew J., and Usami Shin-Ichi. There have been active collaborations between countries, authors, and institutions. The primary research topics focused on genotype-phenotype correlations, genetic screening, diagnostic advancements, and exploration of pathogenic mechanisms. Research on *SLC26A4* gene-related hearing loss has notably increased since 2011, with ongoing clinical investigations and basic research efforts. Future studies may further explore disease mechanisms and potential therapeutic interventions related to the *SLC26A4* gene.

Keywords: *SLC26A4* gene, hearing loss, hotspots, research trends, visualization analysis

1. Introduction

Hearing loss (HL) is a prevalent sensory defect globally, with both syndromic and non-syndromic HL commonly inherited and linked to over 250 genes (*1*). *SLC26A4* gene mutation is one of the leading causes of hereditary HL worldwide (*2*). *SLC26A4* (solute carrier family 26, member 4), also known as PDS, is the causative gene of Pendred syndrome and autosomal recessive nonsyndromic deafness 4 (DFNB4) (*3,4*). Both Pendred syndrome and DFNB4 are associated with enlargement of the vestibular aqueduct and HL. *SLC26A4* encodes pendrin, which is expressed in the inner ear, thyroid gland, and kidney (*3,5,6*). Pendrin functions as an anion exchanger for Cl^-/I^- and Cl^-/HCO_3^- across apical plasma membranes of epithelial cells (*7,8*).

Researchers worldwide have conducted numerous clinical and basic studies on *SLC26A4* gene-related HL (*7*). However, there remains a gap in comprehensively exploring the current research status and future trends of *SLC26A4* in HL through the lens of a scientific knowledge graph. Research in this field has mainly explored specific topics without thoroughly examining research evolution from an international and comprehensive standpoint and without using knowledge graph tools for multi-angle visual research. Moreover, there is a lack of in-depth investigation into research hotspots, emerging frontiers, and evolving topic trends.

This study utilized bibliometric tools including Bibliometrix, CiteSpace, and VOSviewer to analyze and visualize a scientific knowledge map of the *SLC26A4* gene in HL research. International literature published between 1994 and 2023 was retrieved from the Web of Science Core Collection database. In addition, this study analyzed key information in this field, including journals, countries, institutions, authors, keywords, and references. The goal of this study was to assess research hotspots and trends in *SLC26A4* gene research in HL, providing a reference and direction for follow-up research.

2. Materials and Methods

2.1. Data collection

We conducted a comprehensive search of the science citation index expanded (SCI-E) database in the Web of Science Core Collection to obtain all relevant publications. A search query was conducted using the following formula: (TS = "SLC26A4" OR TS = "SLC26A4 gene" OR TS = "Pendred syndrome" OR TS = "Pendred syndrome gene" OR TS = "PDS" OR TS = "PDS gene" OR TS = "large vestibular aqueduct" OR TS = "large vestibular aqueduct syndrome" OR TS = "enlarged vestibular aqueduct" OR TS = "large vestibular canal" OR TS = "large vestibular canal malformation") AND (TS = "hearing" OR TS = "auditory" OR TS = "audiological" OR TS = "audiology" OR TS = "hearing loss" OR TS = "deafness" OR TS = "hearing impairment" OR TS = "hearing disorder" OR TS = "hearing defect" OR TS = "hearing handicap" OR TS = "hearing difficulty").

2.2. Screening criteria

The retrieval period spanned from January 1994 to December 2023, and the search language was limited to English. This search strategy yielded 1,578 records collected on March 25, 2024. Subsequently, we filtered the results by document type to include only articles. Reviews, editorials, letters to the editor, retracted publications, book chapters, meeting abstracts, proceedings, and papers with early access were excluded. After applying the inclusion criteria, 1,308 publications were ultimately included in this study. The study design is illustrated in Figure 1.

2.3. Bibliometric analysis

Bibliometric analysis and visualization were conducted using Bibliometrix (version 4.0.0), CiteSpace (version 6.2.R6), and VOSviewer (version 1.6.20). Bibliometrix is an R package that provides scientific mapping workflow from data collection to data visualization. CiteSpace is a Java-based software made especially for bibliometric network analysis and visualization. VOSviewer is software used to construct and visualize bibliometric networks based on citation, co-citation, co-authorship, or term co-occurrence relations. Multiple points extracted from the dataset were used to conduct the bibliometric analysis, including journals, countries, institutions, authors, keywords, cited references, publication years, titles, abstracts, document types, number of citations, and time of citations. Additionally, the h-index and g-index, two crucial bibliometric metrics for exploring scientific production and impact, were gathered (*9,10*). The data were then imported into the bibliometric tools; Bibliometrix, CiteSpace, and VOSviewer for analysis. Network maps generated by these tools include collaboration networks, co-occurrence, and co-citation (*11,12*).

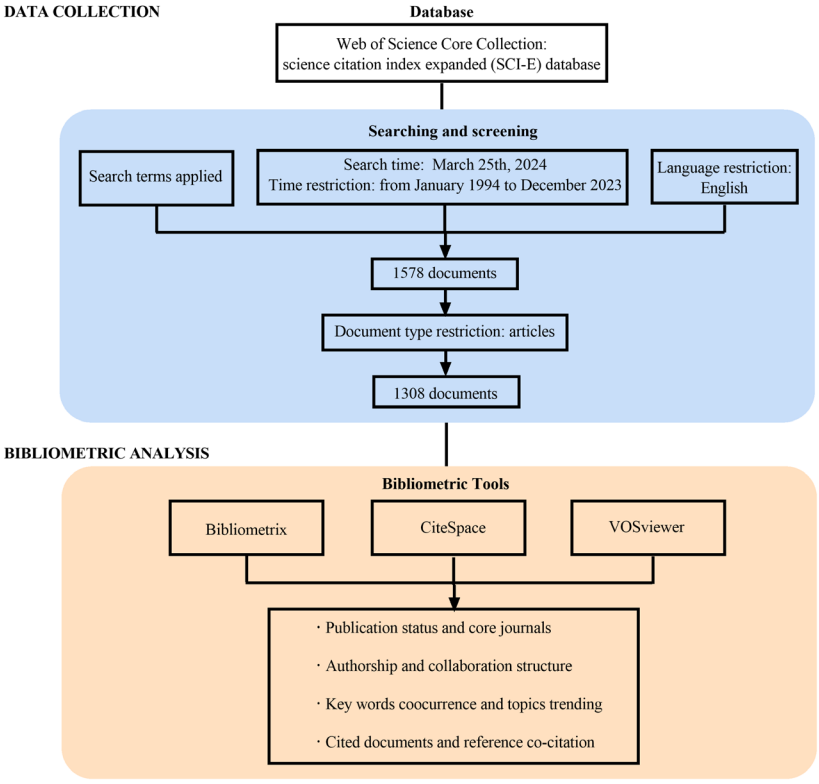

Figure 1. Data collection and bibliometric analysis of this study.

2.4. Statistical analysis

Bibliometrix analysis included key information from the dataset such as annual publications, journal production, publication citations, countries' production, institutions' production, authors' production, cited references, core journals based on Bradford's law, country collaboration maps, author productivity according to Lotka's law, and author's production over time. CiteSpace analysis included collaboration networks and the centrality value of countries, institutions, and authors; keywords with the strongest citation bursts; and the co-citation reference network. VOSviewer was used to generate a co-occurrence network and keyword clusters.

3. Results

3.1. Annual global publication volume

Between 1994 and 2023, 1,308 articles related to *SLC26A4* gene-related HL were published worldwide (Table 1). The annual publication trends show a fluctuating increase, as shown in Figure 2. The number of papers published in 1999, 2001, 2011, 2013, 2016, and 2017 showed rapidly increasing trends. The highest number of publications (NP) (80) was in 2017. The overall increase in publications can be roughly categorized into three stages based on yearly scientific production: the first stage (1994–2010), showing slow and stable development; the second stage (2011–2017), demonstrating continuous and rapid development; and the third stage (2018-2023), indicating a fluctuating trend.

Table 1. Main information from the dataset used in this study after manual screening

Main Information	Details
Timespan	1994-2023
Documents	1,308
Keywords	2,116
Reference	21,197
Countries	62
Institutions	1,515
Authors	5,792
Journals	337
Language	English

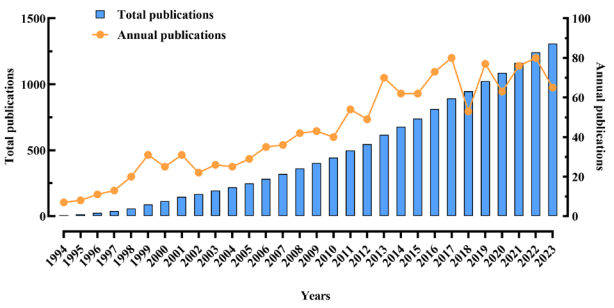

Figure 2. Total publications and annual publication distribution of research on *SLC26A4* gene-related hearing loss from 1994 to 2023. The blue bars represent the accumulation of articles, while the orange line demonstrates the annual scientific production.

3.2. Core journals, authorship, and collaboration

3.2.1. Core journals based on Bradford's law

Bradford's law is an essential and fundamental principle in bibliometric analysis that describes the distribution of scientific publications in journals (*13,14*). The core journals were analyzed using Bradford's law (Supplemental Figure S1, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=236*). The 1,308 articles published in 337 journals, and the top 10 most productive journals are listed in Table 2. These top journals published up to 32.34% (423/1,308) articles and represented only 2.97% (10/337) of all journals. The top 3 journals were the *International Journal of Pediatric Otorhinolaryngology*, *Otology & Neurotology*, and *Acta Oto-Laryngologica*, with 115, 81, and 48 published articles, respectively. Table 2 displays the NP, total citations (TC), h-index, g-index, and core journal categories. *Laryngoscope* ranked first in TC (1792), h-index (24), and g-index (42), while *Ear and Hearing* ranked first in Journal Impact Factor (JIF) quartile (Q1).

3.2.2. Scientific production and cooperation of countries

A total of 62 countries and regions were involved in the publication of research. As shown in Figure 3A, the countries and regions with the top three scientific production in this field are the United States, China, and Japan. The United States ranked first with 329 publications and led in terms of TC (13,548) (Supplemental Table S1, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=236*). Figure 3B displays the average article citation counts for leading scientific nations, with France, the United Kingdom, the USA, and Australia ranking highest.

Cooperation between countries generated by CiteSpace is shown in Figure 3c, and a country collaboration map created *via* Bibliometrix is presented in Supplemental Figure S2 (*https://www.irdrjournal.com/action/getSupplementalData.php?ID=236*). According to the cooperation network, the more visible significant collaborations are the connections between the USA and European countries, such as Italy and Germany, and Asian countries, such as China and Japan. A close cooperation sub-network was observed among European countries.

International cooperation is correlated with the ratio of multiple-country production (MCP) to single-country production (SCP) and can be evaluated by the percentage of MCP in the total NP. The findings of this dataset (Figure 3A; Supplemental Table S1, *https://www.irdrjournal.*

Table 2. Top 10 most productive journals sorted by number of publications

Journals	NP	TC	h-index	g-index	JIF quartile and JCR categories
1. International Journal of Pediatric Otorhinolaryngology	115	1,168	20	34	Q3, Otorhinolaryngology Q4, Pediatrics
2. Otology & Neurotology	81	1,624	24	37	Q3, Otorhinolaryngology Q4, Clinical Neurology
3. Acta Oto-Laryngologica	48	645	15	23	Q4, Otorhinolaryngology
4. Laryngoscope	44	1,792	24	42	Q2, Otorhinolaryngology Q3, Medical, research, and experimental
5. Plos One	40	1,252	21	34	Q2, Multidisciplinary sciences
6. European Archives of Oto-Rhino-Laryngology	25	251	11	15	Q2, Otorhinolaryngology
7. Ear and Hearing	19	251	10	15	Q1, Otorhinolaryngology, Q1,Audiology, and speech-language pathology
8. Journal of Laryngology and Otology	19	221	10	14	Q3, Otorhinolaryngology
9. Annals of Otology, Rhinology, and Laryngology	16	670	13	16	Q4, Otorhinolaryngology
10. Clinical Genetics	16	618	13	16	Q2, Genetics and heredity

NP: number of publications; TC: total citations; JIF: Journal Impact Factor; JCR: Journal Citation Reports.

com/action/getSupplementalData.php?ID=236) show that the countries with the highest cooperation rates are Belgium (43.33%), Germany (35.00%), and the United Kingdom (33.33%). Centrality measures the likelihood of the shortest path passing through a node and reflects its importance in the network. Countries with the top five centralities were the United States (0.65), Germany (0.25), the United Kingdom (0.22), France (0.17), and Italy (0.11), indicating that these five countries also have significant roles in this field (Figure 3C; Supplemental Table S1, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=236*).

3.2.3. Scientific production and cooperation of institutions

The top 10 contributing institutions were located in the USA, South Korea, China, and Japan (Supplemental Table S2, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=236*). Regarding the NP, Harvard University and Harvard Medical School ranked the highest. With regard to the total global citations, the National Institutes of Health (NIH), USA, and the NIH National Institute on Deafness and Other Communication Disorders (NIDCD) take the lead.

The cooperation network of institutions (Figure 4A) demonstrated close collaboration and connections among research institutions focusing on *SLC26A4* gene research in HL. Affiliated institutions from various nations are dispersed and intimately connected across the map, particularly because institutions within the same region collaborate more frequently.

3.2.4. Scientific production and cooperation of authors

Lotka's law is a bibliometric and information science principle that characterizes the productivity distribution of authors on a specific topic (*15*). The authors' productivity using Lotka's law is shown in Supplemental Figure S3 (*https://www.irdrjournal.com/action/getSupplementalData.php?ID=236*). The top three productive authors in terms of NP, TC, and h-index were Dai Pu from China (32, 791, and 15, respectively), Griffith Andrew J. from the USA (29, 1,409, and 20, respectively), and Usami Shin-Ichi from Japan (29, 1,204, and 18, respectively) (Supplemental Table S3, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=236*). According to scientific production over time, the top 10 authors (Supplemental Figure S4, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=236*) are from China, USA, Japan, South Korea, and Taiwan. Griffith Andrew J., Smith Richard J. H., and Usami Shinichi have been active in this field since 1996, 1997, and 1999, respectively. Other researchers joined and contributed development in 2005. By 2008, nine of the top 10 authors were dedicated to this field.

Figure 4B shows the collaboration network map of the authors. Numerous closely connected domestic and international clusters exist within the authors' collaborative networks. The authors were divided into several clusters that exhibited close internal interactions. For instance, Griffith Andrew J. from NIH engaged with research teams in the USA, Japan, South Korea, and Taiwan. Dai Pu, Yuan Yongyi, and Huang Shasha,

Figure 3. Countries' scientific productions and collaboration relationships. (A) Scientific production and international collaboration by countries. MCP represents multiple-country production, and SCP represents single-country production; **(B)** Average article citations by countries; **(C)** Collaboration network of countries. Each node's size represents the citations of each country. Node colors closer to the center indicate earlier publication years, while exterior colors indicate more recent publication years. The purple circle represents the node's centrality ≥ 0.1, and the circle's size is proportional to the centrality value.

from the same institution, were also very close to the collaboration map.

3.3. Research on trending topics

3.3.1. Trending topics derived from keyword co-occurrence and clustering

The most frequent keyword visualization is presented in a word cloud map (Supplemental Figure S5, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=236*). A keyword co-occurrence network was generated using VOSviewer to explore keyword co-occurrence and clustering further. A total of 193 keywords, each with a minimum occurrence of 20, were used to generate the network plot (Figure 5). Using VOSviewer, three clusters — green, blue, and red (Figure 5A) — representing various research topics were identified. Additionally, the average citations of these keywords were generated and displayed in Figure 5B.

3.3.2 Trending topics bursts based on keywords

The top 25 keywords with the strongest citation bursts in research are demonstrated in Supplemental Figure S6, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=236*. The blue line represents the period from 1994 to 2023, while the red line indicates the interval between the burst keywords. The keywords with the highest burst strength over the past 30 years are "large vestibular aqueduct" (13.94), "sensorineural HL" (13.76), and "spectrum" (11.01). Other burst keywords in the last 5 years contain "genotype" (2019–2023), "inner ear malformation" (2019–2023), and "guidelines" (2020–2023). From 1994 to 2003, trending topics included "large vestibular

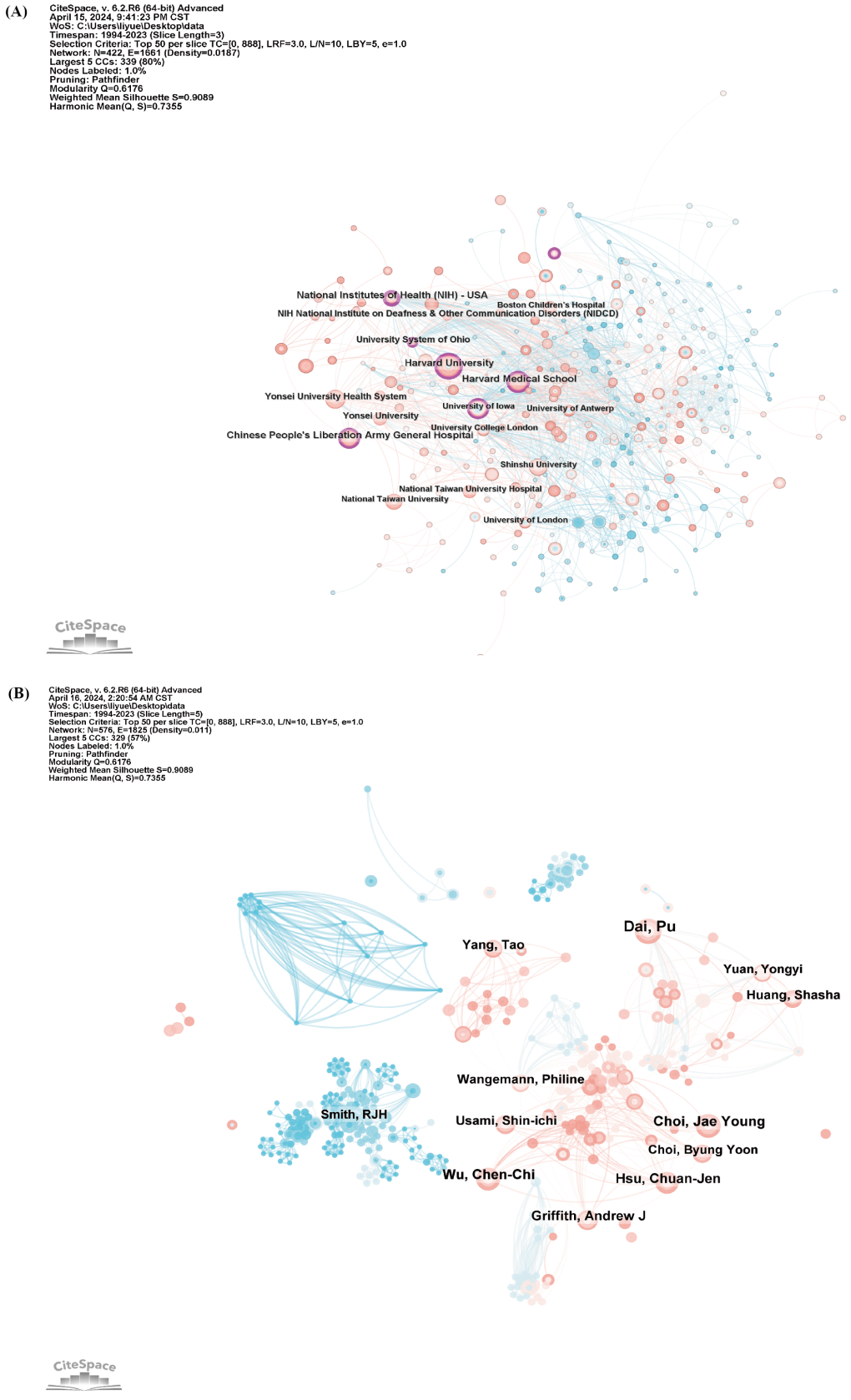

Figure 4. Collaboration network. (A) Institutions' collaboration network. **(B)** Authors' collaboration network. Each node's size represents the citations for each institution or author. Node colors closer to the center indicate earlier publication years, while exterior colors indicate more recent publication years. The purple circle represents the node's centrality ≥ 0.1, and the circle's size is proportional to the centrality value.

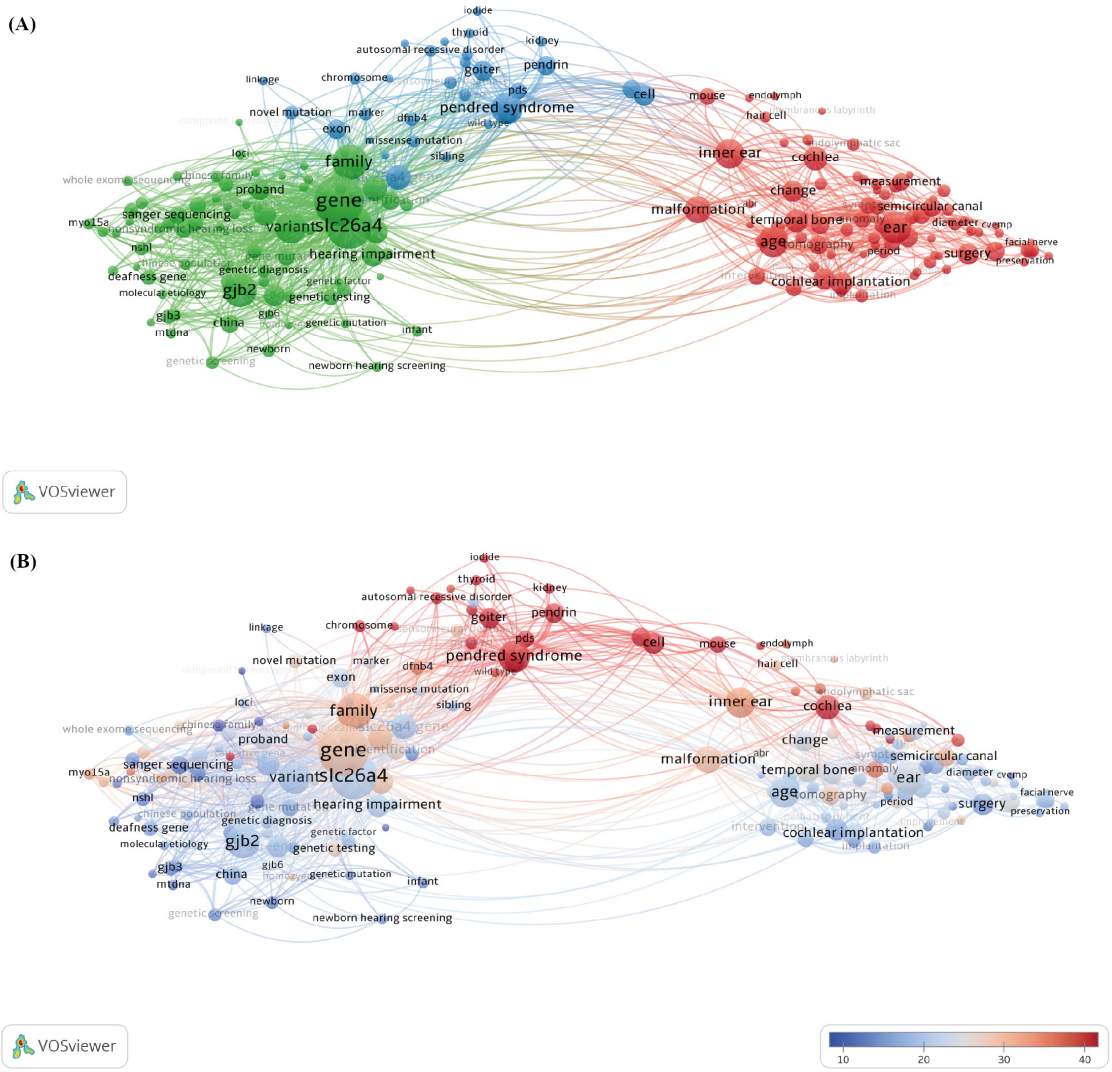

Figure 5. Co-occurrence network of keywords. (A) Clusters; **(B)** Keywords' average citations. Minimum number of occurrences for a term is set at 20, resulting in 193 keywords meeting the threshold. The relative distance between two nodes generally indicates the intensity of their association, and the size of nodes is proportional to the frequency of keywords. Keywords with larger circles indicate research hotspots.

aqueduct", "sensorineural HL", "linkage", and "endolymphatic sac", focusing more on phenotype and tentative anatomical explorations of *SLC26A4* gene-related HL.

3.4. Hotspots derived from publication and reference co-citation

3.4.1. Principal publications

Based on each publication's citation frequency, Bibliometrix was used to determine which articles were the most cited globally. Supplemental Table S4 (*https://www.irdrjournal.com/action/getSupplementalData.php?ID=236*) lists the relevant data for these influential publications. The most globally cited publication was published by Everett *et al*. in 1997 (*3*), focusing on identifying *SLC26A4* gene mutations associated with Pendred syndrome. Three other highly globally cited publications by Scott *et al.* (*16*), Royaux *et al.* (*17*), and Everett *et al.* (*5*) in 1999, 2001, and 2001, respectively, launched new areas of investigation into *SLC26A4* and pendrin proteins, exploring inner ear pathology associated with *SLC26A4* gene mutations through cell experiments and animal models.

3.4.2 Hotspots' evolution trends derived from cited references

Cited references form the scientific foundation of a specific research area (*18*). Supplemental Table S5 (*https://www.irdrjournal.com/action/getSupplementalData.php?ID=236*) presents the top 10 references in the field with the highest citations. The top three cited references are Everett *et al.* (1997) (*3*), Valvassori and Clemis (1978) (*19*), and Park *et al.* (2003) (*2*). These references primarily discuss the mutation frequencies and spectrum of the *SLC26A4*

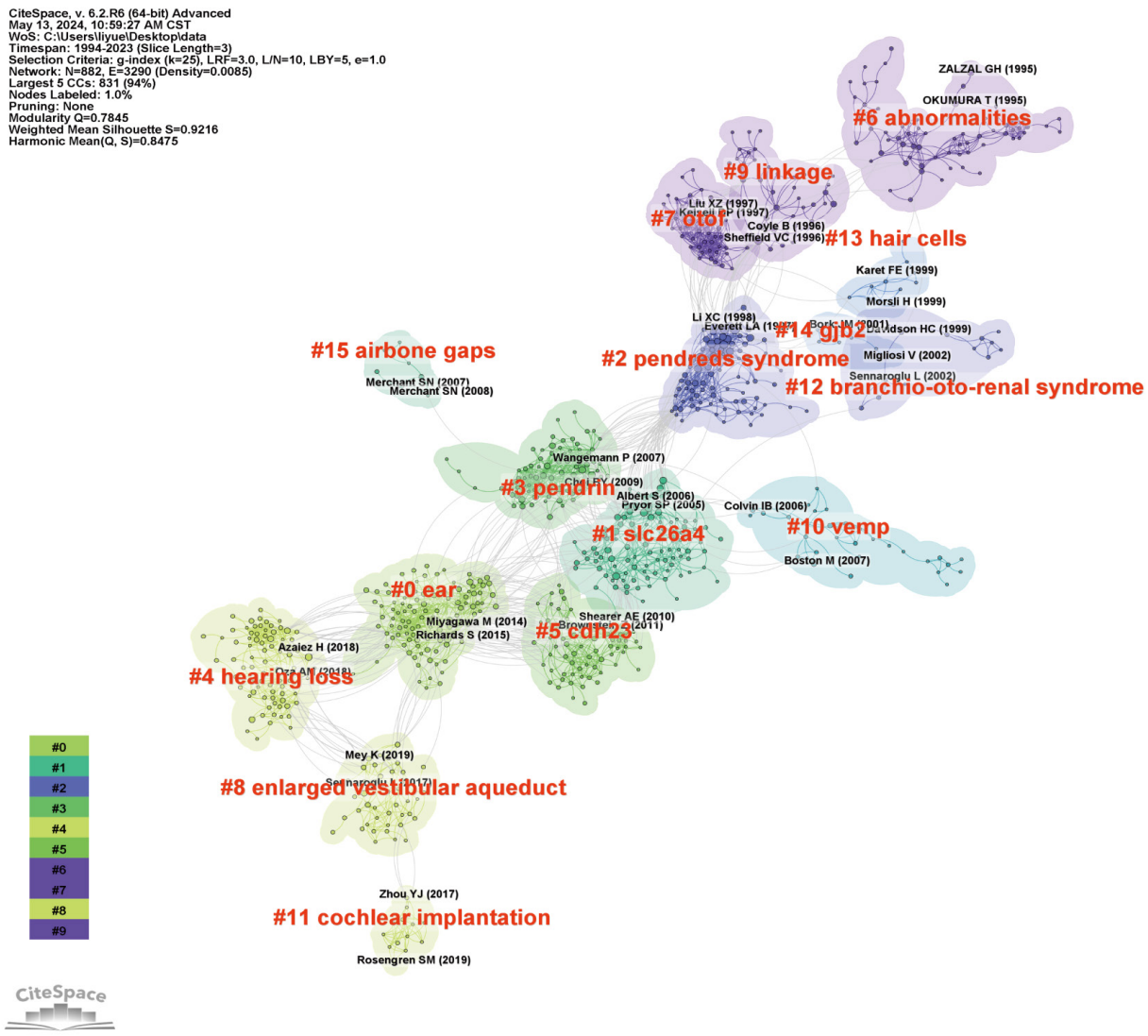

Figure 6. Co-citation reference network with cluster visualization. The size of each node represents the number of citations for each reference.

gene and genotype-phenotype correlations.

To investigate the theoretical underpinnings of the research, we used CiteSpace to create a co-citation network of references. The largest 15 clusters are summarized in Figure 6. Node significance is encapsulated by citation metrics such as counts and bursts, as well as network metrics like betweenness and degree centralities.

The largest cluster (#0) included 110 members and had a silhouette value of 0.853. The most cited members of this cluster are Richards *et al.* (2015) (*20*) and Miyagawa *et al.* (2014) (*21*). The second-largest cluster (#1) had 102 members with a silhouette value of 0.885. The most cited members of this cluster are Pryor *et al.* (2005) (*22*) and Albert *et al.* (2006) (*23*). The third-largest cluster (#2) had 88 members and a silhouette value of 0.915. The most cited members of this cluster are Everett *et al.* (1997) (*3*) and Li *et al.* (1998) (*4*).

4. Discussion

This study utilized bibliometric and visual analysis tools to conduct a comprehensive analysis of research literature on *SLC26A4* gene-related HL within the Web of Science database. A total of 1,308 publications by 5,792 authors from 337 journals were obtained, providing an overview of the research landscape, frontiers, hotspots, and trends. From 1994 to 2023, the annual publications increased with fluctuations in three stages. A rapid increase was observed between 2011 and 2017.

Core journal analysis revealed that *International Journal of Pediatric Otorhinolaryngology* published the most papers. Noteworthy contributions have been made by *Laryngoscope, Ear and Hearing,* and other core journals in terms of TC and JIF. Regarding the TC of publications, Everett *et al.*'s (*3*) publication in *Nature Genetics* was the most frequently cited, with 888 citations.

Approximately 5% of the global population suffers from HL issues, with 3-5% of these cases attributed to mutations in the *SLC26A4* gene, which vary by ethnicity (*24-26*). Studies on nonsyndromic deafness reported biallelic mutations in the *SLC26A4* gene were present in 2% to 3.5% of Caucasian patients (*27-29*), while these mutations frequencies were higher in East Asian patients, ranging from 5.5% to 12.6% (*21,30-32*). The c.716T>A mutation was the most commonly observed in Turkey and Pakistan (*2*), whereas c.1238A>G and c.919-2A>G occurred more frequently as mutations in Iran (*33*,*34*) and c.919-2A>G and c.1334C>T were more commonly found in East Asia (*21,35,36*). Given the wide mutation spectrum of the *SLC26A4* gene, its related hearing loss has attracted global attention, involving researchers from 62 countries. The USA (25.15%), China (23.85%), and Japan (7.34%) ranked among the top three contributing countries, accounting for 56.35% of the total publications. The USA had the most influential impact in this field based on scientific output, average article citations, and cooperation networks. Notably, publications from France, the United Kingdom, and Australia also received high-average article citations, indicating high-quality research. The USA, Germany, the United Kingdom, France, and Italy have had high centrality in recent decades, which indicates that related research in this field from these countries is taking a leading place. Additionally, we found that the rate of international cooperation is generally higher in European countries than in non-European countries and higher in developed countries than developing ones. Contributions in this field from various countries could differ for various reasons, including differences in the ethnicity of patients with HL, diverse cultural backgrounds, financial factors, and medical levels.

Universities and public research institutes are the prominent affiliated institutions involved in research. Research institutions such as the NIH-USA, University of Iowa, NIDCD, University System of Ohio, Harvard University, Harvard Medical School, and the Chinese People's Liberation Army General Hospital contributed to high centrality. Close links were observed in the institutions' collaboration networks, suggesting that international cooperation among institutions is extensive.

Dai (China), Griffith (USA), and Usami (Japan) were the three most productive authors in the field. Griffith, Usami, Smith, and Wangemann each received over 1,000 citations in their publications. The top 15 productive authors were from China, the USA, Japan, Korea, and Taiwan. Compared to countries' collaboration networks and institutions' collaboration networks, we found that authors' collaboration networks showed fewer links and collaborative relationships, indicating potential for strengthening.

Regarding research hotspots, reference co-citation networks reflect the fact that researchers are mainly focused on clinical diagnosis, treatment, intervention, and laboratory research. "The large vestibular aqueduct syndrome" published by Valvassori (1978), is considered a classic reference in this field, analyzing radiographic observations of patients (*19*). Burst keywords reflect emerging trends and research frontiers. Frequent keyword visualizations generated by VOSviewer classify the green, blue, and red clusters into three categories: clinical audiological and genetic diagnosis, genotype-phenotype linkage and mechanical investigation, and clinical treatment. Certain keywords with low frequency (*e.g.*, "iodide", "thyroid", "kidney", "endolymph") received more citations. This finding might indicate that although these topics have received widespread attention from researchers, the number of relevant studies still needs to be improved. The more regularly cited keywords among the more frequently occurring group were "Pendred syndrome", "cochlea", "cell", and "mouse". These keywords are related to clinical symptoms and pathogenic mechanisms. In the last 10 years, research on genotype-phenotype correlations, genetic screening, and diagnosis has progressed rapidly (*7,21,37-39*). Building on this progress, our research group has also focused on *SLC26A4* gene-related hearing loss, including mutation analysis in Chinese families, the investigation of genotype-phenotype characteristics and the prediction models of hearing loss trajectory in children (*40-42*). We identified novel compound heterozygous mutations in *SLC26A4*, as well as mutations in related genes such as *FOXI1* and *KCNJ10* in infants with a single-allele *SLC26A4* mutation (*43,44*).

Around 1999, researchers started to expand the field to include "*PDS* gene", "goiter", "congenital deafness", "molecular analysis", "identification", "sulfate transporter", and "expression", which is more related to mechanism exploration and protein function. Since 1999, basic studies on animal and cell models have proliferated to explore its protein function and pathogenic mechanism (*5,6,16,17,45*). Genetic studies on patients with Pendred syndrome and mouse models have provided insights into the *SLC26A4* gene. However, the exchange mechanism of the *SLC24A4* coding protein, pendrin, remains unknown. With the development of experimental technologies, in 2023, single particle cryo-electron microscopy and anion exchange assays were used to explore the structure and function of pendrin, providing a structural basis for understanding pendrin and *SLC26A4* variants (*46*). A new era of precision gene therapy has emerged (*47*), with recent reports in 2024 of gene therapy for the treatment of children with *OTOF* gene-related HL (*48*). Moreover, several basic research articles have also investigated adeno-associated virus (AAV) gene replacement therapy for recessive hereditary hearing loss involving different genes (*49,50*). Among the datasets we analyzed, we found that there were also explorations into gene therapy with a recombinant adeno-associated virus (rAAV) to transfect *SLC26A4* cDNA in mouse models of *SLC26A4* gene-related HL (*51*), and

another therapy of rescuing *SLC26A4* gene-related HL with *DNAJC14* overexpression *via* Japanese encephalitis virus (JEV) activation (*52*), in mice. In addition, the CRISPR/Cas9-mediated exon skipping strategy (*53*) and the antisense oligonucleotides (ASOs) strategy (*54*) have also been reported to be utilized in mouse models of *SLC26A4* gene-related HL, indicating the feasibility of related therapy and providing a frontier research topic in this field, with potential challenges and opportunities.

There are some limitations to this research: *i*) The literature database we utilized was only the Web of Science, which might have resulted in incomplete literature retrieval; *ii*) Analysis using bibliometric tools such as Bibliometrix, CiteSpace, and VOSviewer might be inconsistent with experts' viewpoints in this field; and *iii*) There might be a selection bias in the publications analyzed.

5. Conclusion

Over the past 30 years, the number of annual publications has generally increased. Researchers from the USA have been the most influential and productive in *SLC6A4* gene research related to HL. Researchers from European and East Asian countries have also contributed significantly to the literature. Genotype-phenotype correlations, as well as genetic screening and diagnosis, are hot spots, alongside basic research on *SLC26A4* gene-related pathogenic mechanisms that have received continuous attention. Future research should focus on gaining deep insights into *SLC26A4* disease-associated mechanisms and therapeutic discoveries.

Funding: This work was supported by the National Natural Science Foundation of China (NSFC) (82071064) and the Capital's Funds for Health Improvement and Research (CFH 2022-2-1092).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. World Health Organization. World report on hearing. *https://www.who.int/publications/i/item/9789240020481* (accessed December 6, 2024).
2. Park HJ, Shaukat S, Liu XZ, *et al.* Origins and frequencies of SLC26A4 (PDS) mutations in East and South Asians: Global implications for the epidemiology of deafness. J Med Genet. 2003; 40:242-248.
3. Everett LA, Glaser B, Beck JC, Buchs IA, Heyman M, Adawi F, Hazani E, Nassir E, Baxevanis AD, Sheffield VC, Green ED. Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). Nat Genet. 1997; 17:411-422.
4. Li XC, Everett LA, Lalwani AK, Desmukh TB, Friedman ED, Wilcox ER. A mutation in PDS causes non-syndromic recessive deafness. Nat Genet. 1998; 18:215-217.
5. Everett LA, Belyantseva IA, Noben-Trauth K, Cantos R, Chen A, Thakkar SI, Hoogstraten-Miller SL, Kachar B, Wu DK, Green ED. Targeted disruption of mouse Pds provides insight about the inner-ear defects encountered in Pendred syndrome. Hum Mol Genet. 2001; 10:153-161.
6. Royaux IE, Belyantseva IA, Wu T, Kachar B, Everett LA, Marcus DC, Green ED. Localization and functional studies of pendrin in the mouse inner ear provide insight about the etiology of deafness in Pendred syndrome. J Assoc Res Otolaryngol. 2003; 4:394-404.
7. Honda K, Griffith AJ. Genetic architecture and phenotypic landscape of SLC26A4-related hearing loss. Hum Genet. 2022; 141:455-464.
8. Lee HJ, Fenollar-Ferrer C, Isgrig K, Wang YX, Valente K, Eide J, Honda K, Chien WW, Petralia RS, Dong L, Friedman TB, Bonifacino JS, Griffith AJ, Roux I. SLC26A4-AP-2 mu2 interaction regulates SLC26A4 plasma membrane abundance in the endolymphatic sac. Sci Adv. 2024; 10:eadm8663.
9. Hirsch JE. An index to quantify an individual's scientific research output. Proc Natl Acad Sci U S A. 2005; 102:16569-16572.
10. Egghe L. Theory and practise of the g-index. Scientometrics. 2006; 69:131-152.
11. Brandes U. A faster algorithm for betweenness centrality. J Math Sociol. 2001; 25:163-177.
12. Chen C. Predictive effects of structural variation on citation counts. J Am Soc Inf Sci Technol. 2012; 63:431-449.
13. Naranan S. Bradford's law of bibliography of science: An interpretation. Nature. 1970; 227:631-632.
14. Venable GT, Shepherd BA, Loftis CM, McClatchy SG, Roberts ML, Fillinger ME, Tansey JB, Klimo P Jr.. Bradford's law: Identification of the core journals for neurosurgery and its subspecialties. J Neurosurg. 2016; 124:569-579.
15. Pao ML. Lotka's law: A testing procedure. Inf Process Manag. 1985; 21:305-320.
16. Scott DA, Wang R, Kreman TM, Sheffield VC, Karniski LP. The Pendred syndrome gene encodes a chloride-iodide transport protein. Nat Genet. 1999; 21:440-443.
17. Royaux IE, Wall SM, Karniski LP, Everett LA, Suzuki K, Knepper MA, Green ED. Pendrin, encoded by the Pendred syndrome gene, resides in the apical region of renal intercalated cells and mediates bicarbonate secretion. Proc Natl Acad Sci U S A. 2001; 98:4221-4226.
18. Chen C. CiteSpace II: Detecting and visualizing emerging trends and transient patterns in scientific literature. J Am Soc Inf Sci Technol. 2006; 57:359-377.
19. Valvassori GE, Clemis JD. The large vestibular aqueduct syndrome. Laryngoscope. 1978; 88:723-728.
20. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015; 17:405-424.
21. Miyagawa M, Nishio SY, Usami S; Deafness Gene Study Consortium. Mutation spectrum and genotype-phenotype correlation of hearing loss patients caused by SLC26A4 mutations in the Japanese: A large cohort study. J Hum Genet. 2014; 59:262-268.
22. Pryor SP, Madeo AC, Reynolds JC, Sarlis NJ, Arnos

KS, Nance WE, Yang Y, Zalewski CK, Brewer CC, Butman JA, Griffith AJ. SLC26A4/PDS genotype-phenotype correlation in hearing loss with enlargement of the vestibular aqueduct (EVA): Evidence that Pendred syndrome and non-syndromic EVA are distinct clinical and genetic entities. J Med Genet. 2005; 42:159-165.
23. Albert S, Blons H, Jonard L, *et al.* SLC26A4 gene is frequently involved in nonsyndromic hearing impairment with enlarged vestibular aqueduct in Caucasian populations. Eur J Hum Genet. 2006; 14:773-779.
24. Bayazit YA, Yilmaz M. An overview of hereditary hearing loss. ORL J Otorhinolaryngol Relat Spec. 2006; 68:57-63.
25. Sloan-Heggen CM, Bierer AO, Shearer AE, *et al*. Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss. Hum Genet. 2016; 135:441-450.
26. Danilchenko VY, Zytsar MV, Maslova EA, Bady-Khoo MS, Barashkov NA, Morozov IV, Bondar AA, Posukh OL. Different rates of the *SLC26A4*-related hearing loss in two indigenous peoples of southern Siberia (Russia). Diagnostics (Basel). 2021; 11:2378.
27. Rendtorff ND, Schrijver I, Lodahl M, Rodriguez Paris J, Johnsen T, Hansén EC, Nickelsen LA, Tümer Z, Fagerheim T, Wetke R, Tranebjaerg L. SLC26A4 mutation frequency and spectrum in 109 Danish Pendred syndrome/DFNB4 probands and a report of nine novel mutations. Clin Genet. 2013; 84:388-391.
28. Dahl HH, Ching TY, Hutchison W, Hou S, Seeto M, Sjahalam-King J. Etiology and audiological outcomes at 3 years for 364 children in Australia. PLoS One. 2013; 8:e59624.
29. Hutchin T, Coy NN, Conlon H, Telford E, Bromelow K, Blaydon D, Taylor G, Coghill E, Brown S, Trembath R, Liu XZ, Bitner-Glindzicz M, Mueller R. Assessment of the genetic causes of recessive childhood non-syndromic deafness in the UK implications for genetic testing. Clin Genet. 2005; 68:506-512.
30. Yuan Y, Guo W, Tang J, Zhang G, Wang G, Han M, Zhang X, Yang S, He DZ, Dai P. Molecular epidemiology and functional assessment of novel allelic variants of SLC26A4 in non-syndromic hearing loss patients with enlarged vestibular aqueduct in China. PLoS One. 2012; 7:e49984.
31. Guo YF, Liu XW, Guan J, Han MK, Wang DY, Zhao YL, Rao SQ, Wang QJ. GJB2, SLC26A4 and mitochondrial DNA A1555G mutations in prelingual deafness in Northern Chinese subjects. Acta Otolaryngol. 2008; 128:297-303.
32. Zhu J, Cao Q, Zhang N, Ge J, Sun D, Feng Q. A study of deafness-related genetic mutations as a basis for strategies to prevent hereditary hearing loss in Hebei, China. Intractable Rare Dis Res. 2015; 4:131-138.
33. Koohiyan M, Hashemzadeh-Chaleshtori M, Tabatabaiefar MA. Molecular diagnosis of *SLC26A4*-related hereditary hearing loss in a group of patients from two provinces of Iran. Intractable Rare Dis Res. 2021; 10:23–30.
34. Yazdanpanahi N, Tabatabaiefar MA, Bagheri N, Azadegan Dehkordi F, Farrokhi E, Hashemzadeh Chaleshtori M. The role and spectrum of SLC26A4 mutations in Iranian patients with autosomal recessive hereditary deafness. Int J Audiol. 2015; 54:124-130.
35. Lee KY, Choi SY, Bae JW, Kim S, Chung KW, Drayna D, Kim UK, Lee SH. Molecular analysis of the GJB2, GJB6 and SLC26A4 genes in Korean deafness patients. Int J Pediatr Otorhinolaryngol. 2008; 72:1301-1309.
36. Ruan Y, Wen C, Cheng X, Zhang W, Zhao L, Xie J, Lu H, Ren Y, Meng F, Li Y, Deng L, Huang L, Han D. Genetic screening of newborns for deafness over 11 years in Beijing, China: More infants could benefit from an expanded program. Biosci Trends. 2024; 18:303-314.
37. Dai P, Huang LH, Wang GJ, *et al.* Concurrent hearing and genetic screening of 180,469 neonates with follow-up in Beijing, China. Am J Hum Genet. 2019; 105:803-812.
38. Li M, Nishio SY, Naruse C, *et al.* Digenic inheritance of mutations in EPHA2 and SLC26A4 in Pendred syndrome. Nat Commun. 2020; 11:1343.
39. Forli F, Lazzerini F, Auletta G, Bruschini L, Berrettini S. Enlarged vestibular aqueduct and Mondini Malformation: audiological, clinical, radiologic and genetic features. Eur Arch Otorhinolaryngol. 2021; 278:2305-2312.
40. Wen C, Wang S, Zhao X, Wang X, Wang X, Cheng X, Huang L. Mutation analysis of the SLC26A4 gene in three Chinese families. Biosci Trends. 2019; 13:441-447.
41. Du Y, Huang L, Wang X, Cui Q, Cheng X, Zhao L, Ni T. Clinical data analysis of genotypes and phenotypes of deafness gene mutations in newborns: A retrospective study. Biosci Trends. 2017; 11:460-468.
42. Deng L, Yang X, Cheng X, Wen C, Yu Y, Li Y, Gao S, Liu H, Liu D, Ruan Y, Xie J, En H, Xian J, Huang L. Hearing loss trajectory and prediction model for children with enlarged vestibular aqueduct. Am J Otolaryngol. 2024; 46:104573.
43. Zhao X, Cheng X, Huang L, Wang X, Wen C, Wang X. Novel compound heterozygous mutations in SLC26A4 gene in a Chinese family with enlarged vestibular aqueduct. Biosci Trends. 2018; 12:502-506.
44. Zhao X, Cheng X, Huang L, Wang X, Wen C, Wang X, Zhao L. Analysis of mutations in the FOXI1 and KCNJ10 genes in infants with a single-allele SLC26A4 mutation. Biosci Trends. 2019; 13:261-266.
45. Rotman-Pikielny P, Hirschberg K, Maruvada P, Suzuki K, Royaux IE, Green ED, Kohn LD, Lippincott-Schwartz J, Yen PM. Retention of pendrin in the endoplasmic reticulum is a major mechanism for Pendred syndrome. Hum Mol Genet. 2002; 11:2625-2633.
46. Liu Q, Zhang X, Huang H, *et al.* Asymmetric pendrin homodimer reveals its molecular mechanism as anion exchanger. Nat Commun. 2023; 14:3012.
47. Schambach A, Buchholz CJ, Torres-Ruiz R, Cichutek K, Morgan M, Trapani I, Büning H. A new age of precision gene therapy. Lancet. 2024; 403:568-582.
48. Lv J, Wang H, Cheng X, *et al*. AAV1-hOTOF gene therapy for autosomal recessive deafness 9: a single-arm trial. Lancet. 2024; 403:2317-2325.
49. Askew C, Chien WW. Adeno-associated virus gene replacement for recessive inner ear dysfunction: Progress and challenges. Hear Res. 2020; 394:107947.
50. Simons EJ, Trapani I. The opportunities and challenges of gene therapy for treatment of inherited forms of vision and hearing loss. Hum Gene Ther. 2023; 34:808-820.
51. Kim MA, Kim SH, Ryu N, Ma JH, Kim YR, Jung J., Hsu CJ, Choi JY, Lee KY, Wangemann P, Bok J, Kim UK. Gene therapy for hereditary hearing loss by SLC26A4 mutations in mice reveals distinct functional roles of pendrin in normal hearing. Theranostics. 2019; 9:7184-7199.
52. Choi HJ, Lee HJ, Choi JY, Jeon IH, Noh B, Devkota S, Lee HW, Eo SK, Choi JY, Lee MG, Jung J. DNAJC14 Ameliorates Inner Ear Degeneration in the DFNB4

Mouse Model. Mol Ther Methods Clin Dev. 2019; 17:188-197.
53. Huang CY, Tsai YH, Cheng YF, Wu PY, Chuang YC, Huang PY, Liu JS, Wu CC, Cheng YF. CRISPR/Cas9-mediated exon skipping to restore premature translation termination in a DFNB4 mouse model. Gene Ther. 2024; 31:531-540.
54. Feng P, Xu Z, Chen J, Liu M, Zhao Y, Wang D, Han L, Wang L, Wan B, Xu X, Li D, Shu Y, Hua Y. Rescue of mis-splicing of a common *SLC26A4* mutant associated with sensorineural hearing loss by antisense oligonucleotides. Mol Ther Nucleic Acids. 2022; 28:280-292.

Received December 6, 2024; Revised January 20, 2025; Accepted January 27, 2025.

**Address correspondence to:*
Lihui Huang, Key Laboratory of Otolaryngology-Head and Neck Surgery, Ministry of Education, Beijing Institute of Otolaryngology, Beijing Tongren Hospital, Capital Medical University, No. 17 Hougou Lane, Chongnei Street, Beijing 100005, China.
E-mail: huanglihui@ccmu.edu.cn

Released online in J-STAGE as advance publication February 1, 2025.