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Genes linked to hearing and vestibular phenotypes in humans and mice: an interspecies systematic review

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Abstract

Mouse models are relevant to study functionality of genes involved in human hearing and vestibular disorders; however, other pre-clinical models including organoids could be more suitable depending on the gene and its homology across species. While some mouse models replicate human hearing phenotypes, models for vestibular disorders like Meniere Disease (MD) are lacking. We aimed to identify genes associated with auditory and vestibular phenotypes (AVP) in humans and mice to prioritize candidate genes for further MD research. A systematic review was conducted extracting data from PubMed, Scopus, the International Mouse Phenotyping Consortium (IMPC), and the Deafness Variation Database (DVD). We included studies reporting AVP linked to genetic variants in human, mice or both. A total of 31 interspecies auditory phenotype genes shared between the IMPC and DVD, of which 25 were expressed in both cochlear and vestibular tissues. Five were prioritized as AVP candidates—*CIB2, COL9A2, CLRN1, GRXCR1, MARVELD2*. IMPC screening also revealed 52 mouse hearing loss genes, several with strong cochlear and vestibular expression not previously described. Integrating phenotypic and expression data highlighted *NIN, CCDC88C, OTOG, CLRN1, GRXCR1,* and *MARVELD2* as promising candidates for MD. Vestibular phenotyping is underrepresented in current KO mouse models, as vestibular function is not systematically tested in the IMPC pipeline, leading to incomplete annotation of vestibular phenotypes. Comprehensive vestibular assessments in IMPC pipelines and targeted vestibular phenotype evaluation of individuals with rare variants in DVD genes are essential to advance translational vestibular research.

Keywords Sensorineural hearing loss, Vestibular dysfunction, International Mouse Phenotyping Consortium, Deafness Variation Database, Meniere disease

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Introduction

Hearing loss is the most prevalent sensory deficit worldwide, affecting approximately 5% of the global population [1]. Sensorineural hearing loss (SNHL) is a heterogenous condition influenced by genetic and environmental variables, with monogenic inheritance accounting for 60% of human cases [2]. During the last decades, the discovery of hearing loss genes has followed two main streams: (i) human studies in large families combining positional cloning and segregation analysis in the past century, and later parallel massive sequencing of small families or trio analysis for singletons with segregation of rare variants found in individuals with hearing loss; (ii) mouse phenotyping of gene knockout models to identify novel mouse genes involved in hearing and vestibular disorders [2, 3]. Although ~ 150 genes have been identified as causal genes of hearing loss, 40–50% of cases remain unresolved [4]. The challenge is even greater for vestibular disorders, where the genetic contribution is poorly understood. Meniere's disease (MD) exemplifies this gap in literature.

Meniere's disease is a multifactorial inner ear disorder characterized by episodic vertigo, fluctuating low-to-mid frequency SNHL, tinnitus, and aural fullness. Familial aggregation has been reported in approximately 6–10% of cases, suggesting a genetic contribution. To date, ~ 20 genes have been reported in Familial MD, with patterns of autosomal dominant (AD), autosomal recessive (AR) and biallelic inheritance. Among these, *TECTA*, *OTOG*, *GJD3D* and *MYO7A* are the most commonly observed genes in the European descendant population [5–7]. Proteins encoded by these genes are essential to the structural integrity of hair cell stereocilia and tectorial membrane in the organ of Corti.

Two major resources provide complementary insights into genetic contributors to auditory phenotypes: the International Mouse Phenotyping Consortium (IMPC) and the Deafness Variation Database (DVD). The IMPC systematically phenotypes knockout mice to elucidate gene function [8, 9], while the DVD curates human genetic variants linked to deafness. However, both lack robust vestibular annotation.

Establishing an interspecies consensus on shared genes contributing to hearing and vestibular impairment is crucial for developing relevant disease models for human SNHL and AVP. This systematic review aimed to identify genes associated with auditory and vestibular phenotypes by searching for Human Phenotype Ontology (HPO) terms—vestibular hypofunction, vestibular dysfunction, (progressive) sensorineural hearing impairment, hearing impairment, functional abnormality of the inner ear, abnormal ear physiology, abnormality of the ear, phenotypic abnormality, and postexertional symptom exacerbation—and comparing genes catalogued in the International Mouse Phenotyping Consortium (IMPC) and Deafness Variation Database (DVD). For this, we have catalogued interspecies genes shared between databases, identified species-specific contributors, and prioritized genes with high cochlear and vestibular expression to provide evidence to design functional studies and the development of pre-clinical models relevant to human SNHL and cochleovestibular disorders such as MD.

Materials and methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10].

Registration and protocol

This review's protocol was registered on PROSPERO (CRD420251029358).

Research question and selection criteria

To investigate the genetic contributors to audiovestibular phenotype (AVP) and identify probable candidate genes for future studies, the subsequent questions were raised.

- Which genes have been identified as associated with auditory or vestibular phenotype in humans?
- Which genes have been found to be associated with auditory or vestibular phenotype in mice?
- What are the interspecies and species-specific genes that contribute to auditory, vestibular or AVP in the respective populations?

To address these queries, the review followed the PICO (Population–Intervention–Comparison–Outcomes) question as outlined:

- Population: patients and mice with auditory or vestibular phenotype
- Intervention: genes identified as contributing to hearing loss or vestibular dysfunction from studies and databases in human and mice populations
- Comparison: healthy controls, individuals and animal models with no auditory or vestibular phenotype
- Outcome: identification of interspecies and species-specific genes contributing to hearing, vestibular or AVP in humans and mice
- Study Design: case–control studies, cohort studies, mouse models studies.

Search strategy

A search strategy was performed on July 1, 2025, for studies published in PubMed and Scopus databases. The MeSH terms used were: *("Sensorineural Hearing Loss"* OR *"Vestibular Dysfunction"*) AND (*Gene OR Genetics*) AND (*Frequency*). Preliminary filtering removed duplicates, non-English studies, reviews and meta-analyses. From

retrieved studies, the following exclusion criteria was employed: single case reports with less than 5 individuals reported, animal studies involving species other than mice, and articles not relevant to the review's objective.

Data extraction and synthesis

Authors, year of publication, study design, species and population studied, number and sex of subjects, ethnicity (human studies only), age, sequencing technique, candidate genes and variants, inheritance pattern, hearing profile and vestibular impairment data were extracted from selected studies.

Gene search utilizing published articles

Further filtering was carried out on selected studies to identify interspecies and species-specific genes of interest. DOIs were retrieved, and three independent reviewers (C.A., N.N., and S.P.) screened the introduction, results and discussion sections of each study using a tailored list composed of genes obtained from the IMPC [8] and DVD [11]. For genes, the Human Genome Organization (HUGO) nomenclature was used, and for protein only the recommended name was employed. Both gene and proteins identifiers were extracted from UniProt to use as search keywords [12]. Studies that replicated hereditary hearing loss in either human or mice populations matching the tailored lists were included.

Data collection

Three independent reviewers (C.A., S.P., and N.N.) extracted the outcomes and key characteristics from all included studies, and the data were compared. When consensus could not be reached, a fourth reviewer (J.A.L.E.) was involved. Relevant studies were selected for the review, and reference information of interest was extracted.

Risk of bias assessment

ROBINS-E and SYRCLE tools [13, 14] were used to assess the risk of bias in non-randomized human and mouse studies, respectively. A table was used to summarize the results using a color-coded scale.

Six ROBINS-E domains were used: (i) confounding-induced bias, (ii) bias in exposure measurement, (iii) bias in participant selection for the study, (v) bias due to missing data, (vi) bias in outcome measurement and (vii) bias in the selection of reported results. Domain (iv) bias resulting from post-exposure interventions was excluded as it was irrelevant to this study. For animal cellular models, items iii, iv and v from SYRCLE were irrelevant and excluded from the analysis.

For studies involving both human and mouse models, a combination of ROBINS-E and SYRCLE's criteria was applied.

Data sources and processing

Through the utilization of two publicly available genomic and phenotypic resources, the identification of candidate genes associated with AVP in humans and mice was performed. Variant interpretation in human followed the ClinGen Hearing Loss Variant Curation Expert Panel (HL-VCEP) guidelines, which adapt the ACMG/AMP criteria for hearing loss-specific variant classification [15].

Auditory and vestibular phenotype data for mouse models were obtained from the IMPC portal. This included auditory brainstem response (ABR) thresholds and vestibular phenotype scores for all available knockout strains. Human hearing loss genetic data were retrieved from the DVD. Vestibular phenotype information for human genes was manually extracted from the Online Mendelian Inheritance in Man (OMIM) database (https://omim.org; accessed on July 1, 2025) [16], based on clinical descriptions of vestibular dysfunction such as vertigo, tinnitus, imbalance, and ataxia.

Gene expression data were extracted from the gEAR portal [17–19] using four publicly available datasets (Supplementary Table S1). The dataset selection met the following criteria (i) flow-cytometry-selected inner ear cell types, (ii) matched developmental stage, and (iii) directly comparable microarray or RNA-seq platforms. Datasets one and two included microarray and RNA sequencing public data from postnatal day 0 and 1 (P0 and P1) mouse auditory and vestibular epithelia. These datasets featured hair cells (HCs,) epithelial non-hair cells (ENHCs) and non-epithelial cells (NECs) from the organ of Corti and vestibular maculae epithelia, separated by flow cytometry [20].

Datasets three and four consisted of adult and P2 mouse cochlear gene expression data respectively, sampled across the apical, middle and basal cochlear turns to evaluate genes involved in tonotopic gradients. These datasets were generated using Agilent Mouse Exon Microarrays technology [21] and validated by quantitative RT-PCR [22].

A log fold-change (logFC) of >1.5 was considered significantly expressed in the tissue of interest. The criteria for defining differentially expressed genes (DEGs) across datasets 1, 2 and 4 were established as follows: $|\text{logFC}| \geq 1.5$.

Dataset three was manually checked against our genes of interest. A log fold-change (logFC) of >1.5 was considered significantly expressed in the tissue of interest. $\log2\text{FC} |\geq 2.0$ and adjusted P-value < 0.05.

Interspecies v. species-specific genes

Genes were classified as interspecies if both human and mouse datasets demonstrated auditory and/or vestibular phenotypes. Genes with phenotypic evidence in only one

species were categorized as species-specific. The interspecies genes were assessed for vestibular expression using the four datasets representing postnatal and adult mouse auditory and vestibular epithelia.

Mouse hearing loss genes

To identify genes with a high likelihood of contributing to auditory or audiovestibular dysfunction in mice, 67 candidate hearing loss genes identified by the IMPC were analyzed [23]. Of these, 52 were not previously recorded to be associated with auditory phenotype in either human or mouse populations and were of interest.

Audiovestibular genes

To identify genes contributing to AVP in both human and mice, candidate genes were characterized based on the presence of both auditory and vestibular phenotypes according to the IMPC knockout datasets. We defined audiovestibular genes if the following criteria were met: (1) Interspecies auditory phenotype evidence from DVD and IMPC (2) Demonstrated auditory and vestibular phenotypes in mouse models (3) Expression in the cochlea and/or vestibular system according to gene expression data retrieved from the gEAR portal [17–19].

Gene homology analysis

To assess whether differences in gene sequence conservation could explain interspecies discrepancies in audiovestibular phenotypes, a pairwise human-mouse homology analysis for species-specific audiovestibular genes was performed. Nucleotide sequences for Homo sapiens orthologs were retrieved from NCBI (RefSeq), and alignments were generated against the Mus musculus genome using the BLAST (blastn) tool. The output of percentage identity, alignment length, and high-scoring segment pairs (HSPs), were manually extracted.

Gene set enrichment analysis

Gene Set Enrichment Analysis (GSEA) was performed on the DEGs using GeneCodis v4.1.7 [24]. The following functional annotations were applied Gene Ontology (GO), Biological Process (BP), GO Cellular Component (CC), and GO Molecular Function (MF). Furthermore, KEGG pathways and CollecTRI transcription factor targets were performed for *Homo Sapiens* and *Mus musculus* species.

Protein–protein interaction gene networks

A pathway enrichment analysis was conducted using DEGs identified within the datasets using the STRING database [25] to explore protein–protein interactions and associated molecular pathways on the *Homo Sapiens* database. Pathways with a P-value < 0.05 were considered statistically significant with a combined medium confidence score of > 4.0. Summated from evidence types 'curated databases', 'experimentally determined' and 'automated text mining'. All identified pathways were manually reviewed, and those not relevant to auditory or vestibular phenotype were excluded to ensure biological relevance to supporting cell function.

Human phenotype ontology

Enrichment of HPO terms was assessed for the gene set. The signal represents the relative representation of a phenotype in the gene set compared to expectation: signal > 1 indicates an overrepresented phenotype, signal = 1 indicates representation as expected by chance, and signal < 1 indicates an underrepresented phenotype.

Audiovestibular genes with potential relevance to meniere disease

To identify genes contributing to audiovestibular phenotypes in both humans and mice, we defined audiovestibular genes using the following criteria. First, genes were required to show interspecies auditory phenotype evidence, defined as the presence of an auditory phenotype in both DVD and IMPC. Second, genes were to demonstrate both auditory and vestibular phenotypes in mouse knockout models, based on ABR threshold elevations and vestibular information reported by the IMPC. Third, genes were required to exhibit expression in cochlear and/or vestibular tissues, determined using transcriptomic datasets accessed through the gEAR portal. A gene was classified as significantly expressed if it met the following log fold-change thresholds: $|\log FC| \geq 1.5$ in datasets 1, 2, and 4, and $\log 2FC \geq 2.0$ with an adjusted $P < 0.05$ in dataset 3.

Results

We selected 454 studies that met the inclusion criteria (Fig. 1). Of the total number of records, 433 were conducted on humans and 15 were conducted on mice (*Mus musculus*). Furthermore, 6 studies contained both human and mice subjects.

Human studies

Out of the 433 articles conducted on humans (Supplementary Table S2), 118 genes were reported. When cross-referenced with the DVD and IMPC gene lists, we identified 78 genes were present only in the DVD, 15 genes were represented in both DVD and IMPC genes, no genes were exclusive to the IMPC list, and 25 genes were not found in either database, and therefore represent potential candidates. Analysis of the hearing profile reported in the studies showed that high-frequency SNHL was the most frequently reported phenotype (n = 74), followed by low-frequency (n = 27) and mid-frequency SNHL (n = 18). Less commonly, studies reported

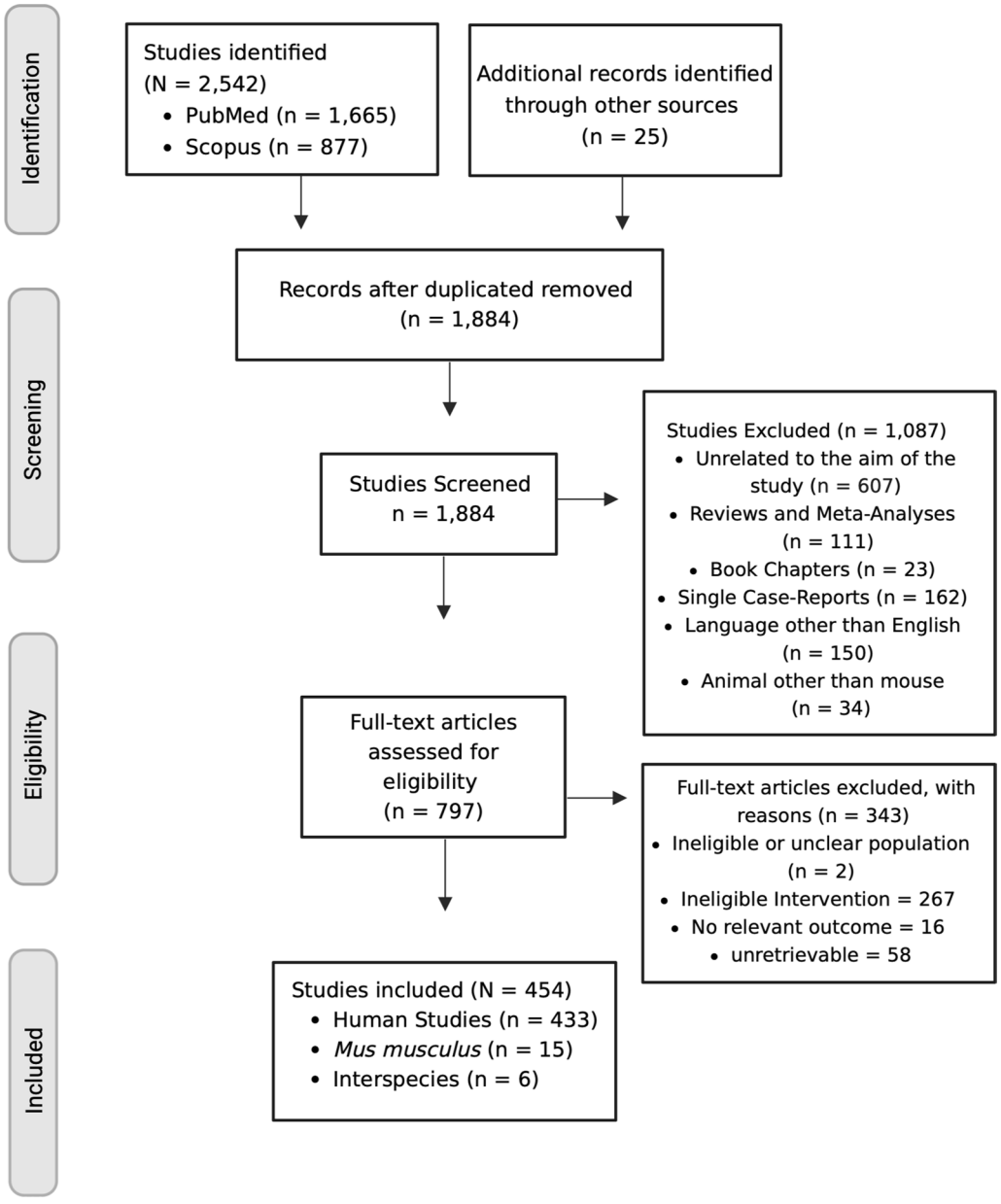


Fig. 1 PRISMA Flow Diagram. Following deduplication, 1884 articles were assessed against eligibility criteria, resulting in 454 articles for inclusion

flat/broadband SNHL (n = 2) or explicitly noted normal/no hearing loss (n = 3).

Vestibular function assessment was inconclusively reported across the included studies. Only 59 out of the 433 studies employed vestibular testing, while the remaining 374 relied on clinical history, symptom questionnaires, or neurological examination without instrumentation. Among those with formal testing, the most common methods included caloric testing (n = 50), vestibular evoked myogenic potentials (VEMPs) (n = 24), video Head Impulse Test (vHIT) (n = 14), and rotary chair (n = 6). Across all studies, abnormal vestibular findings were documented in nine studies using formal testing and in 14 studies using only history or basic clinical examination. In contrast, explicitly normal vestibular function was recorded in three studies with formal testing but was rarely stated in studies relying only on history.

Mice studies

Of the 15 mouse model studies analyzed (Supplementary Table S3), two studies focused on *Myo7a* and *Cdh23*, which in their severe alleles modelled Usher syndrome-like or congenital deafness phenotypes [26, 27]. Seven studies described AR models involving *Ptprq, Grxcr1, Cdh23, Tmc1/2, Klhl18,* and *Myo7a*, with vestibular impairment observed in *Ptprq* null mice, severe balance

and locomotor deficits in *Grxcr1* mutants, and allele-specific hair bundle abnormalities with associated vestibular dysfunction in *Cdh23* [28–34]. Autosomal dominant haploinsufficiency- based models were reported for *Myo7a* and *Chd7*, both associated with low–mid frequency hearing loss, with *Myo7a* mutants also showing hyperactivity, spinning and head-bobbing indicative of vestibular involvement [34, 35]. Other auditory genes with recessive to semidominant inheritance including *Ceacam16, Atp2b2* and *Tbx1,* produced complex AVPs [32, 36]. Among these, *Klhl18* mutants showed progressive low-frequency hearing loss, *Atp2b2* variants produced semidominant progressive high-frequency hearing loss without vestibular deficits, and *Tbx1* caused complete deafness accompanied by severe vestibular malformations and behavioural abnormalities. Additionally, five studies expanded on late-onset or dominant phenotypes, with *Coch* knockin models mimicking human DFNA9 showing progressive high-frequency hearing loss by 21 months and vestibular deficits detectable months before auditory decline using Vestibular Evoked Potentials [37, 38], *Tectb* knockouts selectively impairing low-frequency hearing without vestibular testing [39], a *Gjb2* dominant-negative model producing outer hair cell dysfunction but no systematic vestibular assessment [40], and *Fgfr3* mice exhibiting incomplete penetrance, predominantly low-frequency SNHL but lacking vestibular evaluation [41].

Interspecies studies

Six studies involving human subjects and mice were identified (Supplementary Table S4) [42–47]. Five genes were reported *KLC2, MPZL2, DIAPH1, PTPRQ,* and *COL11A2*. Across species, hearing phenotypes were consistent, with low-frequency SNHL for *KLC2*, high-frequency progressive loss for *MPZL2*, congenital or early-onset SNHL for *DIAPH1* and *COL11A2*. Vestibular findings were limited. In humans, only *MPZL2* carriers were evaluated through rotatory and caloric tests, cervical VEMPs, and vHIT, which showed normal vestibular function. The remaining studies relied on history or clinical examination only. In mice, vestibular phenotyping beyond ABR thresholds was rare. *PTPRQ* was the only study reporting dedicated vestibular assays in animals, with knockout mice showing absent vestibular-evoked potentials and abnormal swimming behaviour—findings not observed in affected humans. *COL11A2* reported weak or absent caloric responses in a subset of individuals but otherwise asymptomatic vestibular function.

Risk of bias assessment

Human and mice risk of bias analyses are summarized in Supplementary Tables S5–S7.

Interspecies and species-specific genes

A total of 331 *Mus musculus* genes associated with auditory phenotypes according to ABR thresholds in IMPC, and 222 human genes in the DVD were linked to hearing loss. Of these, 31 genes were present in both datasets (Supplementary Table S8, Figs. 2A, 2C).

The comparison of P0-P1 microarray and RNAseq datasets revealed that 25 of the 31 interspecies genes were expressed across cochlear and vestibular HC and ENHC. Within the vestibular system, *MYO6, OTOG, OTOGL, COL9A3,* and *SLC17A8* showed high expression in both vestibular HC and vestibular ENHC. Balanced cochlear and vestibular expression was observed for *CABP2, CHSY1, COL9A2, EPS8L2,* and *MPZL2.*

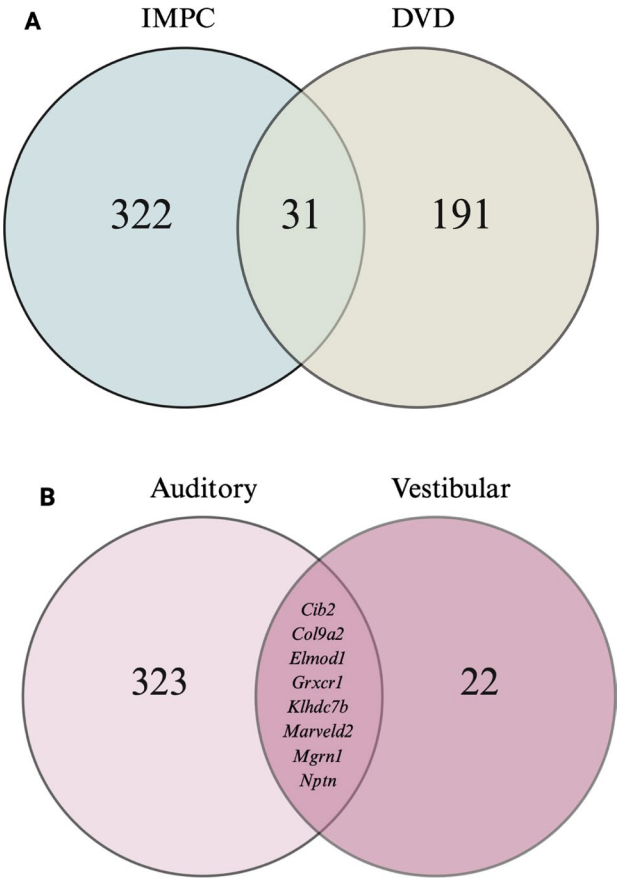
The dataset examining tonotopic gradients across apical, middle, and basal turns of adult 6-week-old mouse cochlea (dataset 3) illustrated that out of the 31 interspecies genes, only five genes *CABP2*, *CLRN1*, *GRXCR1*, *OTOG* and *SLC17A8* showed expression, each with expression levels in the apex and middle turns. *GRXCR1* displayed the highest apex-specific expression (log2 (FC) = 3.92, adj. $p < 0.001$). *CABP2* showed moderate enrichment in the middle turn (log2 (FC) = 2.03, adj. $p = 8.26 \times 10^{-4}$), with *CLRN1* and *GRXCR1* also expressed but at lower levels than in the apex. No genes met significance in the basal turn.

Finally, the dataset of P2 quantitative RT-PCR (dataset 4), provided expression values for apex vs. middle, middle vs. basal, and apex vs. basal turns. Of the interspecies gene set, only *CLRN1*, *GJB3*, and *MYO6* met the $|\log FC| \geq 1.5$ threshold in at least one cell type. *CLRN1* showed expression in inner hair cells, outer hair cells, and Deiters' cells, with lower levels in border and pillar cells. *GJB3* displayed more modest but widespread expression, peaking in Deiters' and pillar cells. *MYO6* was expressed in inner hair cells and outer hair cells, with moderate levels in Deiters' and pillar cells.

Species-specific genes were also identified, with 322 murine and 191 human auditory genes (Fig. 2A). No human-specific vestibular dysfunction genes were found, whereas 30 vestibular genes were identified in mice. Eight of which, *Cib2, Col9a2, Elmod1, Grxcr1, Klhdc7b, Marveld2, Mgrn1* and *Nptn* have audiovestibular evidence according to the IMPC (Fig. 2B).

Mouse hearing loss genes

The IMPCs large-scale auditory screen of 3,006 knockout mouse strains identified 67 candidate hearing loss genes through automated statistical analysis and manual curation, based on significant elevated ABR thresholds relative to wild-type controls matched for strain, sex, and age. Of these, 15 genes had previously documented auditory phenotype associations in either mice or humans, based on the Online Catalog of Human Genes and Genetic



C Classification of 31 Interspecies Genes

Stereocilia-TM	Non-Stereocilia
ADGRV1	*CABP2*
CIB2	*CHSY1*
CLRN1	*CLPP*
EPS8L2	*GIPC3*
GRXCR1	*GJB3*
MYO3A	*HARS2*
MYO6	*HOMER2*
OTOA	*HOXA2*
OTOG	*HSD17B4*
OTOGL	*KCNE1*
TPRN	*MARVELD2*
TRIOBP	*MIR96*
COL9A3	*MPZL2*
COL9A2	*NR2F1*
PJVK	*REST*
	SLC17A8

Fig. 2 Venn diagram illustrating gene set overlaps: **A** Interspecies and species-specific genes identified from Deafness Variation Database (DVD) and the International Mouse Phenotyping Consortium (IMPC); **B** Auditory, vestibular and audiovestibular phenotype-contributing genes identified from IMPC knockout datasets. **C** List of interspecies genes classified according to the location in apical pole of the hair cell stereocilia/ tectorial membrane region

Disorders (OMIM), Mouse Genome Informatics (MGI), and PubMed. The remaining 52 genes were not previously linked to hearing loss in either species. ABR testing in adult mice at 14 weeks of age was performed across five frequencies (6, 12, 18, 24, and 30 kHz). Based on the affected frequency ranges, the 67 candidate genes were grouped based on frequency of hearing loss. 13 genes exhibited high-frequency HL, 10 genes low-frequency HL, 25 genes with severe HL and 19 with mild-HL [23].

To evaluate these genes, gEAR expression analysis was conducted. Across P0-P1 microarray and RNA-seq datasets (dataset 1 and 2), 43 of the 67 genes displayed measurable expression in at least one dataset. Several demonstrated notably high cochlear hair cell expression (*A730017C20Rik, Nedd4l*, Ush*1c*, *Tprn Klc2* and *Eps8l-1*hair), and four genes, (*A730017C20Rik*, *Nedd4l*, *Ush1c*, and *Tprn)*, exhibited high expression in both cochlear and vestibular compartments.

In the dataset examining tonotopic gradients in adult 6-week-old mouse cochlea (dataset 3), seven genes met the $|\log_2 FC| \geq 2.0$ threshold in at least one turn. *Ocm* displayed significant enrichment in the apex compared to the middle turn ($\log_2 FC = 3.76$, adj. $p = 2.14 \times 10^{-4}$), while *Tmem30a* showed marked differences in apex versus basal and middle versus basal comparisons. Other genes, including *Gpr152* and *Elmod1*, exhibited more moderate apex–base gradients, suggesting potential spatially restricted roles in frequency tuning. No genes were detected in the P2 qRT-PCR dataset (dataset 4), consistent with minimal or absent expression at this developmental stage in the examined cochlear cell types.

Audiovestibular genes

The IMPC abnormal ear morphology phenotype identified 30 significant genes contributing to vestibular dysfunction in mice. Of these, eight genes (*Cib2, Col9a2,*

Elmod1, Grxcr1, Klhdc7b, Marveld2, Mgrn1, and *Nptn*) also displayed auditory phenotypes in the murine model (Fig. 2B; Supplementary Table S9). Five genes (*Cib2, Col9a2, Clrn1, Grxcr1,* and *Marveld2*) met the interspecies inclusion criteria and were therefore characterized as candidate interspecies audiovestibular genes warranted for further analysis. gEAR expression analysis of P0–P1 cochlear and vestibular datasets (dataset 1 and 2) demonstrated robust expression in cochlear HCs for *Cib2*, *Clrn1*, *Grxcr1*, and *Marveld2*, with each also showing high expression in vestibular hair cells. *Col9a2* exhibited lower expression in cochlear hair cells and vestibular hair cells but showed strong enrichment in epithelial non-hair cells.

Functionally, IMPC phenotyping data indicate that *Cib2*, *Col9a2*, *Clrn1*, and *Marveld2* have severe ABR threshold elevations across all tested frequencies in mice. In contrast, *Grxcr1*, a recessive mouse hearing loss gene, produced a significant threshold shift at the mid-frequency 12 kHz. However, given its combined AVP and established human DFNB linkage, *GRXCR1* remains a candidate.

Gene homology analysis

BLAST analyses comparing *CIB2, COL9A2, ELMOD1, GRXCR1, KLHDC7B, MARVELD2, MGRN1,* and *NPTN* with their *Mus musculus* orthologues revealed strong overall conservation across all loci examined (Supplementary Table S10). Each gene demonstrated clear alignment to the mouse genome within conserved coding regions, supporting the preservation of core molecular functions across species. *CIB2* showed complete alignment across its queried region, consistent with its well-established role in hair-bundle function. *COL9A2* aligned within its collagen-encoding domains, reflecting the evolutionary stability of collagen IX sequences involved in tectorial membrane structure. *ELMOD1* displayed alignment across regions corresponding to its conserved ELMO/ARF-GAP functional domains that contribute to intracellular signaling and hair-cell maturation. *GRXCR1* exhibited the most extensive conservation, aligning across key regions required for stereocilia rootlet formation and consistent with its known involvement in recessive forms of human hearing loss. *KLHDC7B* demonstrated more restricted but still clearly orthologous alignment across annotated kelch-repeat regions. The tight-junction gene *MARVELD2* showed broad alignment spanning its membrane-associated domains, in line with the high evolutionary conservation of tricellulin and related epithelial barrier proteins. *MGRN1* displayed conserved alignment across exons encoding its ubiquitin-ligase domains, while *NPTN* produced multiple matches across mouse genomic clones and transcripts, reaffirming conserved orthology across diverse assemblies. Collectively, these BLAST results demonstrate cross-species conservation of the eight IMPC supported audiovestibular genes and indicate that primary sequence divergence is unlikely to explain human–mouse differences in audiovestibular phenotype expression.

Gene expression profiles retrieved from the gEAR portal show differential expression across cochlear and vestibular epithelia at postnatal and adult stages (Supplementary Tables S11-13). Sixty-eight DEGs in P0 mouse auditory and vestibular epithelia were identified when comparing hair cells, epithelial non-hair cells, and non-epithelial cells (Fig. 3A). Using a logFC threshold > 1.5, 12 genes *Cabp2, Clrn1, Grxcr1, Otog, Slc17a8, Elmod1, Ocm, Ush1c, Tox, Slc4a10, Gpr152,* and *Nin* were significantly expressed across the tonotopic axis of the cochlea. Of these, 11 genes demonstrated an apex–middle expression pattern in the P2 mouse cochlea, whereas *Slc4a10* displayed a middle–basal expression profile (Fig. 3B). Finally, *Clrn1, Gjb3,* and *Myo6* were differentially expressed, indicating maturation-dependent shifts in cochlear gene expression in the adult 6-week mouse cochlea (Fig. 3C).

Auditory brainstem response for candidate genes

Manual curation of the ABR threshold data for each of the 71 DEGs was performed to identify robust auditory phenotypes across six test frequencies (click, 6, 12, 18, 24, and 30 kHz) (Supplementary Table S14; Supplementary Fig. 1). Mutant strains with inconsistent thresholds between sexes or exhibiting isolated single-frequency threshold elevations were excluded. Using these criteria, the remaining DEGs were classified into four broad categories of hearing loss: low-frequency hearing loss (n = 6), high-frequency hearing loss (n = 14), mild hearing loss (n = 35), and severe hearing loss (n = 16). Low-frequency loss mutants displayed threshold elevations at click and 6 kHz but retained near-normal thresholds at higher frequencies. High-frequency loss mutants showed normal click and 6 kHz responses but progressively higher thresholds above 18 kHz, consistent with basal cochlear vulnerability. Mild hearing loss mutants demonstrated modest but broad-spectrum threshold shifts across all test frequencies. Severe hearing loss mutants displayed profound threshold elevations across the entire frequency range, in several cases approaching the upper measurement limits of the ABR assay.

GO and KEGG functional enrichment analysis

A Gene Set Enrichment Analysis was performed on 71 DEGs. In *Homo sapiens*, the top three enriched pathways for GO_BP (Supplementary Table S15) were "sensory perception of sound" (p-value adjusted [p-val adjusted] = 1.99×10^{-19}; Relative Enrichment [RE] = 29.68), "auditory receptor cell stereocilium

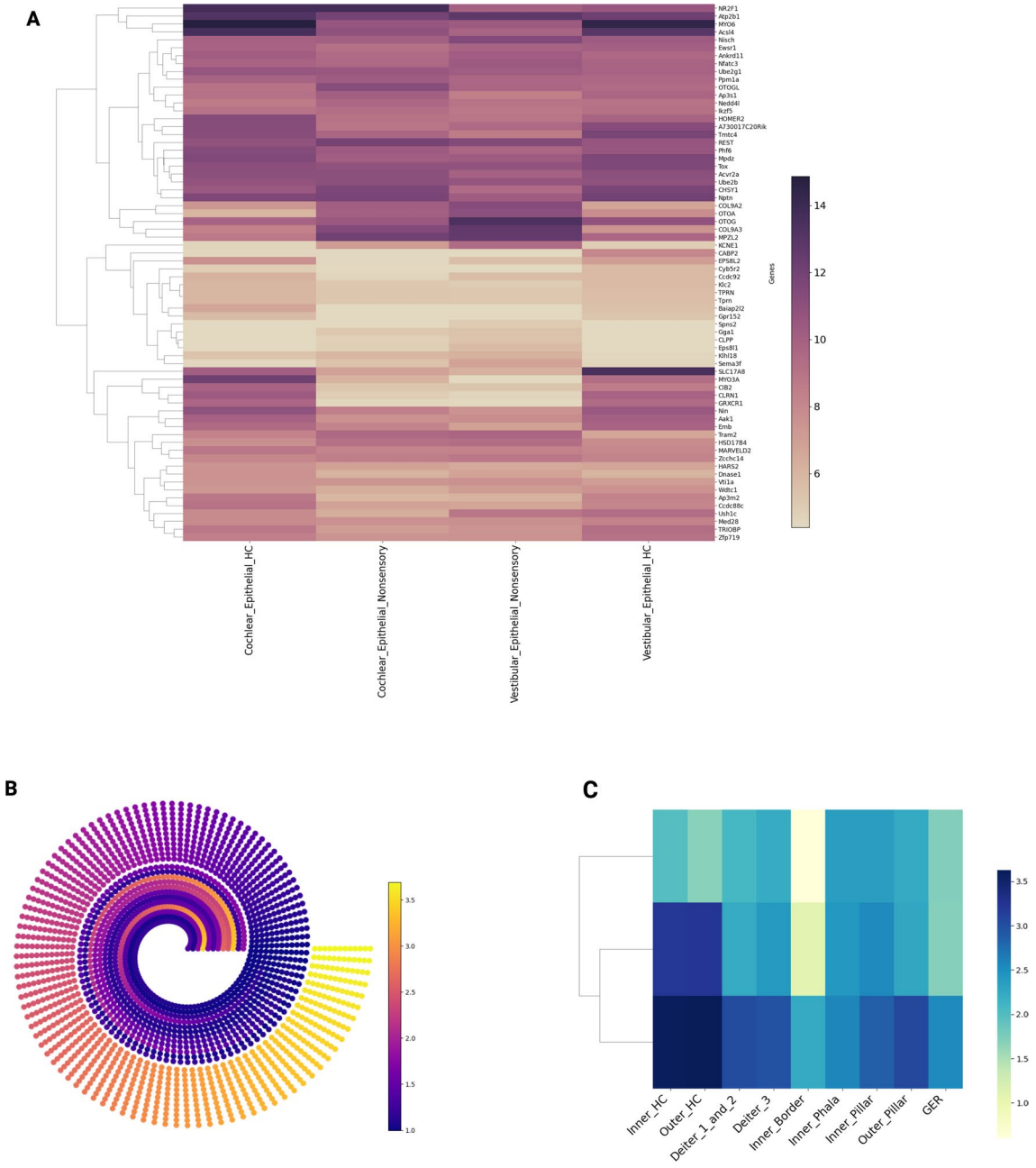


Fig. 3 **A** Heatmap of differentially expressed candidate genes across cochlear and vestibular epithelia using microarray and RNA-seq datasets at postnatal day 0–1 (P0–P1); **B** Spiral heatmap of 12 genes with significant microarray expression (logFC > 1.5) across the tonotopic apex, middle, base organization of P2 mouse cochlea; **C** Heatmap of three genes (*Clrn1*, *Gjb3*, and *Myo6*) differentially expressed in the adult mouse cochlea. Expression values represent log fold-change ($\log_2$ FC) relative to controls

organization" (p-val adjusted = 2.30×10^{-04}; RE = 51.82) and "inner ear receptor cell stereocilium organization" (p-val adjusted = 4.42×10^{-04}; RE = 40.31). The top three enriched pathways for GO_CC (Supplementary Table S16) were "stereocilium" (p-val adjusted = 2.19×10^{-09}; RE = 43.03), "stereocilium tip" (p-val adjusted = 7.44×10^{-05}; RE = 54.30) and "microvillus" (p-val adjusted = 4.08×10^{-04}; RE = 19.00). The significant enriched pathways for GO_MF (Supplementary Table S17) were "actin binding" (p-val adjusted = 1.22×10^{-03}; RE = 6.35) and "alpha-L-arabinofuranosidase activity" (p-val adjusted = 1.22×10^{-03}; RE = 273.57).

Neither KEGG nor collecTRI predicted any significant pathway (Supplementary Table S18), or transcription factors (Supplementary Table S19).

In *Mus musculus*, the top three enriched pathways for GO_BP (Supplementary Table S20) were "sensory perception of sound" (p-val adjusted = 6.88e-[16]; RE = 22.27),

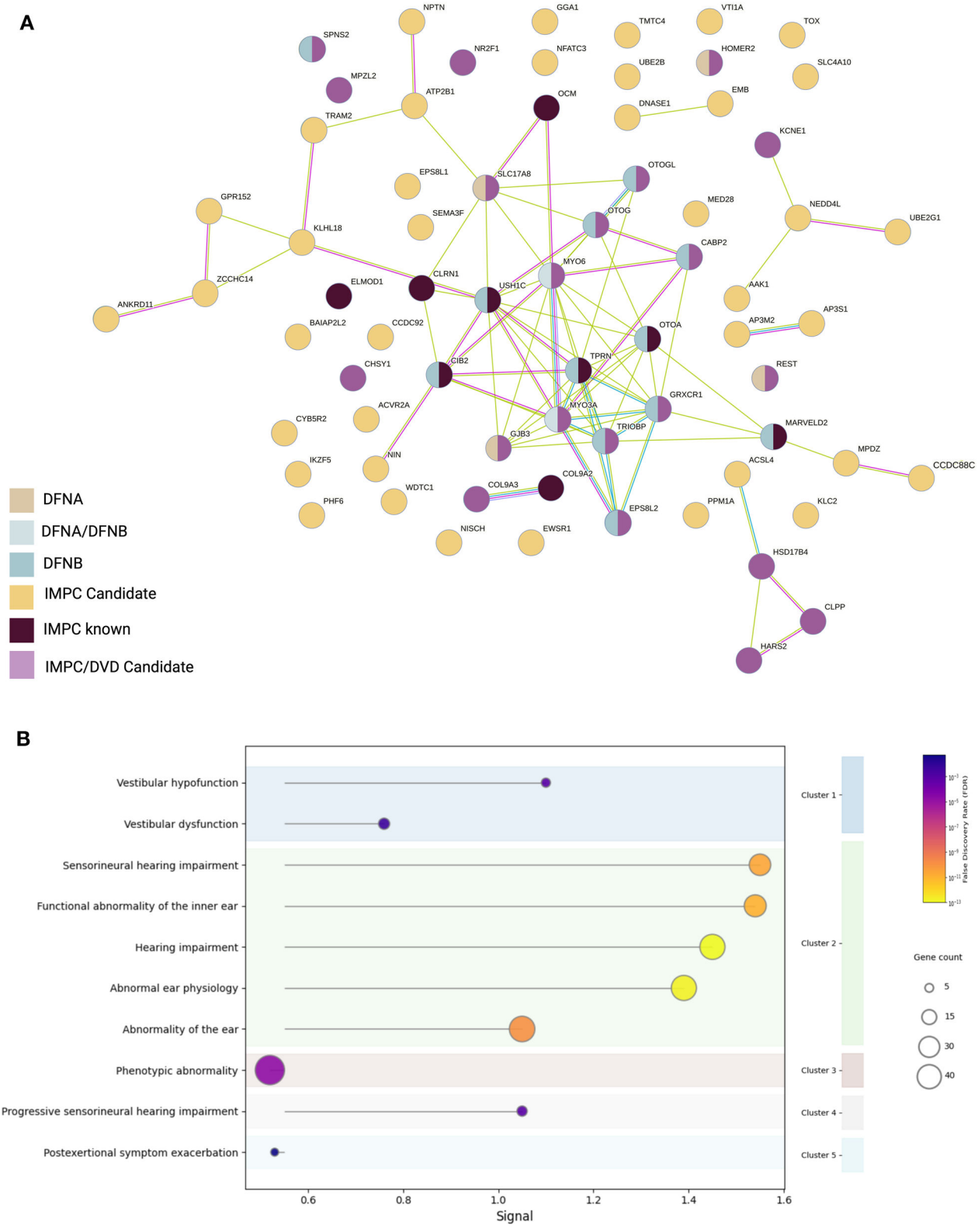


Fig. 4 (See legend on next page.)

(See figure on previous page.)

Fig. 4 Integrated analysis of candidate gene interactions and auditory function. **A** STRING protein–protein interaction (PPI) map of 71 differentially expressed genes (DEGs) in *Homo Sapiens*. Nodes represent proteins, and edges indicate known or predicted interactions (confidence score ≥ 0.4, summated from evidence types: 'curated databases'; 'experimentally determined'; and 'automated text mining'). Additional nodes correspond to previously reported human hereditary hearing loss genes, including DFNA (autosomal dominant), DFNB (autosomal recessive) and DFNA/DFNB (genes with both dominant and recessive inheritance). **B** Human Phenotype Ontology (HPO) enrichment of DEGs. Significant terms included sensorineural hearing impairment, functional abnormality of the inner ear, vestibular hypofunction, and vestibular dysfunction. Size corresponds to the number of associated genes, and color indicates the false discovery rate (FDR). **C** STRING PPI map of orthologous candidate genes in *Mus musculus*. Nodes represent mouse protein-coding genes corresponding to DEGs, and edges denote known or predicted interactions (confidence score ≥ 0.4, based on curated databases, experimental evidence, and automated text mining)

"auditory receptor cell stereocilium organization" (p-val adjusted = 2.08e-^{06}; RE = 71.52), "inner ear receptor cell stereocilium organization" (p-val adjusted = 3.98e-^{04}; RE = 43.35). The top three enriched pathways for GO_CC (Supplementary Table S21) were "stereocilium" (p-val adjusted = 1.31e-^{11}; RE = 54.64), "stereocilium tip" (p-val adjusted = 2.72e-^{05}; RE = 70.54), "apical part of cell" (p-val adjusted = 1.35e^{-} ^{04}; RE = 15.22). The top three significant enriched pathways for GO_MF (Supplementary Table S22) were "actin binding" (p-val adjusted = 2.46e^{-} ^{04}; RE = 8.30), "alpha-L-arabinofuranosidase activity" (p-val adjusted = 7.09e^{-04}; RE = 362.28), "actin filament binding" (p-val adjusted = 2.50e^{-02}; RE = 8.05).

Neither KEGG nor collecTRI predicted any significant pathway (Supplementary Table S23), or transcription factors (Supplementary Table S24).

It is worth noting that the gene count was always below 50% in the GO, KEGG or collecTRI analyses across species.

Protein–protein interaction networks and pathways

The dominant component (Fig. 4A) of the protein–protein interaction (PPI) network generated by STRING in *Homo Sapiens* consisted of 83 nodes and 178 edges. Within the dominant network, five peripheral subclusters were identified: (i) stereocilia and synaptic machinery (*CIB2, MYO6, MYO3A, TPRN, GRXCR1*); (ii) extracellular matrix and collagen (*COL9A2, COL9A3, OTOG, OTOGL, OTOA*); (iii) vesicular trafficking and adaptor proteins (*AP3M2, AP3S1, TRAM2, NEDD4L, AAK1*); (iv) mitochondrial and metabolic enzymes (*CLPP, HARS2, HSD17B4, ACSL4*); and (v) bridging genes (*USH1C, EPS8L2*) connecting subclusters into a cohesive interactome. Central hub genes *CABP2, CIB2, MYO6,* and *MYO3A* showed the highest connectivity.

Within the core module, four genes *CABP2, CIB2, MYO6* and *MYO3A* were identified as central hubs, exhibiting the highest number of direct interactions and interacted between subclusters (Supplementary Table S25). High-confidence edges included *COL9A2-COL9A3* (0.99), *AP3M2-AP3S1* (0.991), *OTOA-OTOG* (0.955).

Within the dominant STRING component, five distinct subclusters were evident in the periphery, each defined by their interaction density. First, a stereocilia and synaptic machinery cluster, comprised of *CIB2, MYO6, MYO3A, TPRN,* and *GRXCR1*. Within this cluster, *MYO6-TPRN* (0.715) represented the strongest interaction. *MYO6-CIB2* (0.46), *MYO3A-TPRN* (0.77), *CIB2-MYO3A* (0.452), *CIB2-GRXCR1* (0.425) and *GRXCR1-TPRN* (0.928) were also observed.

A second extracellular matrix and collagen cluster included *COL9A2, COL9A3, OTOG, OTOGL,* and *OTOA*. The highest confidence interactions within this cluster were *COL9A2–COL9A3* (0.99), *OTOG–OTOGL* (0.899), and *OTOA–OTOG* (0.955). Additional edges included *CABP2–OTOG* (0.487).

The third vesicular trafficking and adaptor protein cluster composed of *AP3M2, AP3S1, TRAM2, NEDD4L* and *AAK1*. The central edge was *AP3M2–AP3S1* (0.991). Further interactions included *AAK1–NEDD4L* (0.412) and *ATP2B1–TRAM2* (0.426).

A fourth mitochondrial and metabolic enzyme cluster included *CLPP, HARS2, HSD17B4* and *ACSL4* which grouped together through moderate-confidence interactions. *CLPP–HSD17B4* (0.719) represented the strongest edge. Additional links included *HARS2–CLPP* (0.57) and *ACSL4–HSD17B4* (0.459).

Finally, two bridging genes, *USH1C* and *EPS8L2*, linked these peripheral subclusters into a cohesive interactome. Notable interactions included *USH1C-CLRN1* (0.909), *USH1C-CIB2* (0.819), *EPS8L2-MYO3A* (0.917) and *EPS8L2-TRIOBP* (0.634).

The DEGs were significantly enriched for auditory-related biological processes, including sensory perception of sound (FDR = 2.8×10^{-19}), inner ear receptor cell differentiation (FDR = 2.1×10^{-6}), and stereocilium organization (FDR = 1.6×10^{-5}). Reactome pathway analysis demonstrated strong enrichment for sensory processing of sound by inner hair cells (FDR = 6.8×10^{-9}) and outer hair cells of the cochlea (FDR = 3.2×10^{-8}). GO Cellular Component terms confirmed subcellular localization to the stereocilium (FDR = 2.2×10^{-9}), stereocilium tip (FDR = 7.4×10^{-5}), and actin-based cell projections (FDR = 4.6×10^{-6}), consistent with structural specialization of auditory hair cells.

Human Phenotype Ontology (HPO) enrichment illustrated strong translational relevance (Supplementary Table S26), with significant associations for sensorineural hearing impairment (FDR = 2.1×10^{-11}), inner ear abnormalities (FDR = 1.1×10^{-11}), and vestibular hypofunction

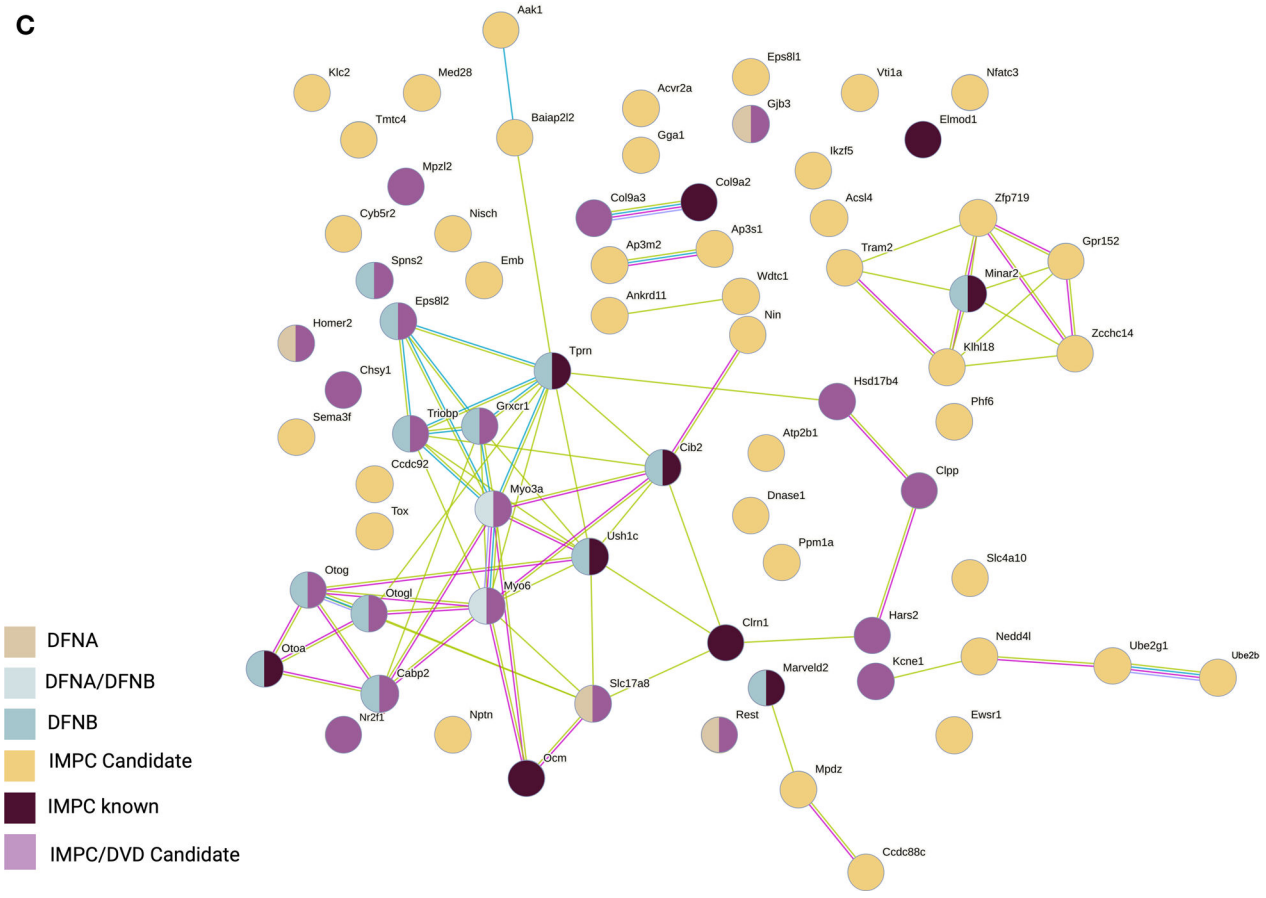


Fig. 4 (continued)

(FDR = 3.0×10^{-4}). Six genes were enriched for vestibular dysfunction, *GJB3, MYO6, CLRN1, USH1C, CIB2, OTOGL*. Notably, four genes—*CLRN1, USH1C, CIB2, and OTOGL*—were specifically implicated in vestibular hypofunction, suggesting an AVP (Fig. 4B). Keyword enrichment further emphasized auditory disease relevance, with deafness (FDR = 2.5×10^{-25}), hearing (FDR = 5.3×10^{-13}), and cell junctions (FDR = 4.0×10^{-3}) as dominant categories.

The dominant STRING component of the *Mus musculus* PPI network formed a cohesive interactome organized into several tightly connected subclusters reflecting core auditory processes (Fig. 4C, Supplementary Table S27). A stereocilia–synaptic machinery module, centered *on Myo6, Myo3a, Cib2, Ush1c, Grxcr1* and *Eps8l2*, displayed the highest internal connectivity, with strong edges such as *Grxcr1–Tprn* (0.929), *Myo3a–Myo6* (0.853), and *Eps8l2–Myo3a* (0.929), underscoring their roles as structural and mechanotransduction hubs. A second extracellular matrix/tectorial membrane cluster comprising *Col9a2, Col9a3, Otog, Otogl,* and *Otoa* featured hallmark interactions including *Col9a2–Col9a3* (0.97) and *Otog–Otogl* (0.899). Additional peripheral modules included a vesicular trafficking cluster built around *Ap3m2–Ap3s1* (0.976) and associated regulators *Nedd4l, Klhl18,* and *Tram2*, as well as a mitochondrial metabolic cluster linking *Clpp, Hars2,* and *Hsd17b4*. Bridging adaptor proteins such as *USH1C* and *EPS8L2* connected peripheral modules to the central stereocilia network, integrating membrane, cytoskeletal, and synaptic processes. Across the interactome, *Myo6, Myo3a, Cib2, Ush1c, Grxcr1,* and *Eps8l2* constituted the principal network hubs, reflecting conserved auditory architecture between human and mouse PPI networks.

Comparing *Homo Sapiens* and *Mus musculus* PPI maps revealed a strongly conserved core interactome centered on stereocilia and mechanotransduction machinery. In both species, *MYO6, MYO3A, CIB2, USH1C, GRXCR1, TPRN,* and *TRIOBP* formed the principal hubs, creating a dense structural module linking stereocilia rootlets, actin-based projections, and synaptic components. The extracellular matrix and tectorial membrane cluster comprising of *COL9A2, COL9A3, OTOG, OTOGL,* and *OTOA* were also conserved, with similar high-confidence interactions seen through *COL9A2–COL9A3* and *OTOG–OTOGL*. Likewise, the vesicular trafficking module centered on *AP3M2–AP3S1* appeared in both networks. Species-specific differences were confined

primarily to the periphery. The *Homo Sapiens* network incorporated additional regulatory deafness genes such as *GJB3, REST,* and *HOMER2*, whereas the mouse network demonstrated a more prominent adaptor and trafficking submodule involving *KLHL18, ZFP719, GPR152,* and *MINAR2*. Despite these peripheral differences, the overall modular architecture, hub structure, and key interaction pathways were highly conserved across species.

Discussion

This study combines a systematic review of genes associated with hearing loss with the DVD and IMPC databases to prioritize candidate genes for the molecular diagnosis of hearing and vestibular disorders. Several gaps have been identified including the human-mouse interspecies differences and most important the incomplete vestibular phenotyping of KO mouse and individuals with hearing loss in clinical research studies.

Mouse-human genomic databases

Rare genetic variants contribute significantly to AVPs. The HL-VCEP has refined 28 criteria for genetic HL, tailored for nine representative genes: *USH2A, SLC26A4, GJB2, MYO7A, CDH23, TECTA, COCH, KCNQ4,* and *MYO6* [15]. To address the challenge of accurately classifying and functionally validating rare and novel variants contributing to AVPs, an interspecies comparative approach across pathogenicity levels is valuable. The IMPC enables functional interrogation of gene knockouts across 163 physiological parameters per *Mus musculus*, offering insights into gene-level pathogenicity through complete loss-of-function [9]. In contrast, the DVD catalogues over 876,000 human variants implicated in hereditary hearing loss, with 96% classified as rare or novel [11]. Of these, more than 8,000 are deemed pathogenic or likely pathogenic, while the majority remain of uncertain significance. By comparing full knockouts in mice, a representation of extreme pathogenicity, with graded variant pathogenicity in humans, ranging from benign to pathogenic, we are able to infer which genes and variants warrant further functional or clinical investigation in the context of AVDs. In this review, we analysed studies that investigated gene expression in SNHL cohorts. These studies included both human and mouse models and described over 118 genes in total.

Interspecies and species-specific genes

We identified 31 interspecies auditory phenotype genes, of which 25 were expressed in both cochlear and vestibular tissues. This overlap underscores the high conservation of auditory mechanisms between mice and humans. However, discrepancies in vestibular phenotyping remain. For example, *PTPRQ* variants in humans caused prelingual bilateral SNHL —two cases were congenitally deaf and two had severe loss—yet no formal vestibular testing was performed [48]. By contrast, *Ptprq*$^{-}$/$^{-}$ mice, also profoundly deaf, underwent detailed vestibular evaluation. Vestibular Evoked Potentials revealed absent or elevated thresholds, and behavioural assays (reaching reflex, rotarod, swimming) showed circling, rolling, and delayed righting responses indicative of vestibular dysfunction [28]. These species-specific differences likely reflect both biological divergence and the limited vestibular assessment performed in some human studies.

Mouse hearing loss genes

IMPC auditory screening identified 67 candidate hearing loss genes, including 52 genes not previously associated with auditory dysfunction. Expression analyses highlighted *A730017C20Rik, NEDD4L, USH1C, TPRN, KLC2, and EPS8L1* as candidates with high cochlear and vestibular enrichment, suggesting dual roles in balance and hearing. Tonotopic gradients in *OCM, TMEM30A, and ELMOD1* further support their potential involvement in frequency-specific hearing. These findings expand the genetic landscape of hearing loss, though further validation is required to confirm their translational significance.

Biological pathways and protein–protein interaction networks

Audiovestibular candidate genes, *CIB2, COL9A2, CLRN1, GRXCR1,* and *MARVELD2,* demonstrated robust cross-species evidence, supported by IMPC phenotyping, expression in vestibular hair cells, and network analyses. In STRING protein–protein interaction mapping, *CABP2, CIB2, MYO6,* and *MYO3A* emerged as central hubs, while *COL9A2, COL9A3, OTOG, OTOGL,* and *OTOA* clustered within extracellular matrix interactions essential for tectorial and otolithic membrane integrity. These networks highlight how dysfunction in stereocilia organization, synaptic machinery, or extracellular matrix proteins may converge to produce AVPs.

Candidate genes for Meniere disease

Meniere Disease is a chronic inner ear disorder characterized by episodic vertigo, fluctuating SNHL, tinnitus, and aural fullness. Although the majority of MD cases are sporadic, approximately 10% display familial aggregation, suggesting a strong genetic contribution to disease pathogenesis. To date, more than 20 genes have been implicated, with AD, and compound heterozygous recessive inheritance. Despite these advances, the genetic architecture of MD remains incompletely understood, and many rare variants remain as uncertain significance.

Our findings reinforce the contribution of established MD-associated genes while highlighting additional

candidates with strong interspecies and expression support. *OTOG* emerged as the most frequent gene in familial MD, consistent with its structural role in the tectorial and otolithic membranes. Disruption of otogelin compromises coupling between sensory epithelia and extracellular matrices, leading to both auditory and vestibular dysfunction. Similarly, *CLRN1* and *GRXCR1* demonstrated overlapping evidence across human cohorts, murine knockout models, and transcriptomic datasets. While vestibular impairment has not been documented in human *GRXCR1* variants, knockout mice exhibit pronounced imbalance and head-bobbing phenotypes, suggesting potential species differences in phenotype penetrance. *MARVELD2*, encoding a tight-junction protein, was enriched for rare variants in sporadic MD cohorts and showed strong vestibular expression, supporting its prioritization as an audiovestibular candidate.

In addition to these established genes, we have identified *NIN* and *CCDC88C* as novel MD candidate genes. Both genes displayed robust expression in vestibular tissues and are functionally linked to cytoskeletal and centrosomal organization, processes essential for stereocilia stability and cellular polarity in sensory hair cells. In an independent study, Parra-Perez et al. (2025) have identified a burden of rare variants in *NIN* and *CCDC88C* in a cohort of 287 individuals with sporadic MD [49]. Its absence from previous MD studies underscores the value of combining cross-species phenotypic data with transcriptomic profiling to uncover new contributors to inner ear pathology. *NTN4* and *CLDN14* also emerged as candidates from human cohort studies, where rare missense variants were enriched in sporadic MD cases [50, 51]. These genes implicate axon guidance and tight-junction integrity, respectively, as additional molecular pathways that may underlie disease susceptibility. In summary, these results expand the repertoire of candidate MD genes, linking extracellular matrix genes such as *OTOG* with novel structural and signalling regulators *NIN* and *CCDC88C*. Importantly, they highlight the underrepresentation of vestibular phenotyping in mouse pipelines, which remains a critical barrier to validating audiovestibular candidate genes. Incorporating comprehensive vestibular assessments into large-scale knockout programs, alongside targeted phenotyping of high-expression candidates, will be essential to advancing translational research in MD.

Study limitations

This systematic review has its limitations. First, our analysis is based on previously published literature and publicly available genomic and phenotypic resources. Although these datasets provide valuable insights into potential gene-phenotype relationships, experimental validation remains necessary to confirm causality and biological relevance. Available transcriptomic datasets do not distinguish between semicircular canal and otolith organs, restricting interpretation of end-organ-specific dysfunction. An experimental or in silico validation of these genes and variants through protein or cellular models is needed. Second, our search strategy employed broad vestibular terminology to maximise sensitivity to the lack of consistent vestibular phenotyping terminology, however this approach may have filtered studies reporting more granular vestibular outcomes. Future reviews incorporating multiple-end-organ specific search terms may capture additional candidate genes. Third, this review did not address the contribution of mitochondrial DNA (mtDNA) to AVP. No parallel systematic mtDNA studies exist in mice, and neither the IMPC nor DVD currently annotate mtDNA variants. Future research should investigate whether mtDNA-driven cochleovestibular phenotypes are conserved across species, as this could uncover additional disease mechanisms. Finally, differences between *Homo sapiens* and *Mus musculus* phenotypes may reflect true biological divergence.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40246-025-00891-x.

Supplementary material 1.

Supplementary Material 2. Supplementary Figure: Auditory Brainstem Response (ABR) audiograms for 71 differentially expressed genes (DEGs), showing auditory thresholds (dB SPL) at six frequencies (CLICK, 6, 12, 18, 24, and 30 kHz). Genes were grouped into four categories of hearing loss: severe, mild, high-frequency, and low-frequency. For each category, the black line indicates the median auditory thresholds of female wild-type (WT) control mice. Black dotted line indicates the median auditory thresholds of male WT mice

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Author contributions

C.A. Conceptualization, methodology, data curation, formal analysis, visualization, and writing—original draft. S.P. Screening, validation, figure curation, and writing—review. N.N. Screening and writing—review. J.A.L.E. Supervision, conceptualization, funding acquisition, and writing—review and editing.

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Data availability

The authors have used publicly available data from Elkon et al., 2015, Yoshimura et al., 2014 and Waldhaus et al., 2015.

Declarations

Competing interests

The authors declare no competing interests.

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