Autosomal Recessive Nonsyndromic Hearing Loss 59 (DFNB59) — Comprehensive Disease Report

Causal gene: *PJVK* (pejvakin). Autosomal Recessive Nonsyndromic Hearing Loss 59 (DFNB59; MONDO:0012445; OMIM #610220) is a Mendelian, autosomal recessive sensorineural hearing impairment caused by biallelic loss-of-function variants in ***PJVK*** (HGNC:28015; Ensembl ENSG00000204311), which encodes the 352-residue protein **pejvakin** (UniProt Q0ZLH3), a member of the gasdermin family and paralog of DFNA5/GSDME. The gene maps to chromosome **2q31.2** (GRCh38 chr2:178,451,346–178,462,102; 7 exons). The disease was first defined as the **first human nonsyndromic deafness due to a neuronal (auditory-pathway) defect** (Delmaghani et al., Nat Genet 2006, P 16804542), and its hallmark is striking phenotypic heterogeneity, ranging from pure cochlear sensorineural hearing loss to retrocochlear **auditory neuropathy spectrum disorder (ANSD)**.

> Note on identity: The name is a serial number ("...59") and must not be confused with other DFNB loci. This report follows the specified identifiers (MONDO:0012445, OMIM:610220, gene *PJVK*). Evidence is predominantly human clinical/genetic (consanguineous families, cohort screens) and mouse model organism studies, with supporting in vitro and computational (gnomAD) data.

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1. Disease Information

- **Overview:** DFNB59 is a rare, early-onset (usually prelingual), bilateral, symmetric sensorineural hearing loss. Audiologically it presents either as cochlear-type hearing loss or as ANSD (preserved otoacoustic emissions/cochlear microphonic with absent or abnormal auditory brainstem responses), reflecting pejvakin's role in both sensory hair cells and afferent auditory neurons

(P 16804542). P 28089576

- **Key identifiers:**
- OMIM: **#610220** (phenotype); *PJVK*/DFNB59 gene ***610219**
- MONDO: **MONDO:0012445**
- Orphanet: subsumed under "Rare genetic deafness" / autosomal recessive nonsyndromic sensorineural deafness (no DFNB59-specific ORPHA code widely used); rare disease
- ICD-10: **H90.3** (sensorineural hearing loss, bilateral); ICD-11: **AB52** (sensorineural hearing impairment)
- MeSH: closest terms "Deafness/genetics", "Hearing Loss, Sensorineural", "Auditory Neuropathy" (no DFNB59-specific descriptor)
- HGNC: **PJVK (HGNC:28015)**; gene aliases: DFNB59
- **Synonyms:** DFNB59; deafness, autosomal recessive 59; PJVK-related autosomal recessive nonsyndromic deafness; autosomal recessive auditory neuropathy (AUNB1 historical usage).
- **Information source:** Derived from **aggregated disease-level resources** (OMIM, gene/variant databases) and **individual-patient reports** (consanguineous families, cohort studies); no EHR-scale datasets. Source types: human clinical/genetic, mouse models, in vitro.

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2. Etiology

- **Primary cause: Monogenic / genetic.** Biallelic (homozygous or compound heterozygous) pathogenic variants in *PJVK* cause loss of pejvakin function
(P 16804542). P 22617256
Not infectious, not environmental in origin.
- **Genetic risk factors:** The causal variants themselves (see §4). **Consanguinity** is the dominant risk amplifier, producing homozygosity for rare recessive alleles; most reported families are consanguineous (Iranian, Pakistani, Turkish, Moroccan, Chinese, Spanish)

(P 22617256 P 25631766 P 30582396). P 39107234

- **Environmental risk / modifying factors:** No environmental factor *causes* DFNB59, but **noise/sound exposure is a critical disease-modifying factor**: pejvakin-deficient hair cells and neurons are hypervulnerable to sound, and ambient acoustic load worsens the phenotype (Pjvk−/− mouse hearing thresholds correlated with pups-per-cage) (P 26544938). Ototoxic exposures and aging would be expected to compound an already oxidative-stress-vulnerable cochlea (inferred).
- **Protective factors:** No specific human protective alleles identified. Mechanistically, **reduced acoustic/oxidative-stress exposure** and antioxidant capacity are protective in principle (inferred from the oxidative-stress mechanism; P 26544938). A single functional *PJVK* allele is fully protective (recessive; carriers unaffected) — consistent with gnomAD LoF tolerance (pLI≈0).
- **Gene–environment interaction:** The defining feature of DFNB59 is a ***PJVK* genotype × sound-exposure interaction**: without pejvakin, normally innocuous sound triggers unopposed oxidative damage because the adaptive peroxisome/pexophagy antioxidant response fails (P 26544938 P 30936319). GO:0010498 proteasomal/autophagic terms and CHEBI:26523 reactive oxygen species are relevant.

3. Phenotypes

Core phenotype = **bilateral sensorineural hearing loss** (symptom/clinical sign; laboratory/audiometric abnormality).

Phenotype	Type	Onset	Severity	Progression	Frequency	HPO
Sensorineural hearing loss, bilateral	Clinical sign / audiometric	Congenital/ prelingual (usually)	Moderate→profound	Stable **or** progressive (allele-dependent)	~100%	**HP:0** (SNH HP:0 (hea impa
Auditory neuropathy spectrum disorder (abnormal ABR, preserved OAE/CM)	Lab/ electrophysiologic	Congenital	Variable	Variable	Subset	**HP:0** (abn ABR) HP:0 (con not appl
Progressive hearing loss (e.g., p.C343S family)	Clinical course	Childhood	Severe	Progressive	Subset	**HP:0** (prog SNH
Prelingual / congenital onset	Temporal	Neonatal–childhood	—	—	Majority	**HP:0** (con SNH
Vestibular function	Clinical	—	Generally normal in humans (nonsyndromic)	—	Rare/none	HP:0 regio (vest stud mou mod

- **Severity/course:** Variable and allele-dependent — some patients have **stable severe-to-profound** loss

(P 35052489), others **progressive** loss (P 22617256). Conditional mouse data show early-onset profound loss with complete loss, vs slowly progressive loss with adult-onset OHC degeneration (P 28089576).

- **Quality-of-life impact:** Prelingual severe-to-profound deafness impairs speech/language acquisition, education, and communication; early amplification or cochlear implantation substantially improves outcomes (P 35052489). No DFNB59-specific EQ-5D/SF-36 data; generic sensorineural-deafness QoL instruments apply.
- **Non-otologic features:** None — DFNB59 is **nonsyndromic** (no retinal, renal, cardiac, or neurologic involvement).

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4. Genetic / Molecular Information

- **Causal gene:** ***PJVK*** (DFNB59), OMIM *610219; HGNC:28015; Ensembl ENSG00000204311; 2q31.2; 7 exons. Protein pejvakin, 352 aa, UniProt Q0ZLH3; gasdermin-family (DFNA5/GSDME paralog) with an N-terminal gasdermin/"chaperone"-like domain, a predicted zinc-finger region, and C-terminal cysteines (C328, C343) (P 16804542). P 30936319
- **Pathogenic variants (representative, germline):**
- **Missense:** p.Arg183Trp (c.547C>T; founder-type, used in first knock-in mouse), p.Thr54Ile, p.Gly292Arg (c.874G>A; knock-in mouse), p.Cys343Ser (c.1028G>C; progressive HL), p.Leu224Arg, p.His294Asp (P 16804542

P 22617256

P 32917362

P 35052489

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P 30582396

- **Nonsense:** p.Arg167* (and other truncating alleles).
- **Frameshift:** p.Cys312Trpfs*19 (c.930_931delAC, in zinc-finger domain), p.His294Ilefs*43, p.Phe317Serfs*20

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- **Variant classification:** Reported alleles are **Pathogenic/Likely Pathogenic** (ACMG/AMP) in ClinVar; co-segregation in consanguineous families + absence in controls + conservation support pathogenicity

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- **Allele frequency:** All pathogenic alleles are **very rare/private** in gnomAD/1000G (consistent with founder/consanguineous occurrence). PJVK gnomAD constraint: **pLI≈1.3e-10, oe_lof=0.88, LoF Z=0.63, missense Z=0.08** → LoF-tolerant, as expected for a recessive gene.
- **Origin: Germline** (not somatic; not in COSMIC as a cancer driver).
- **Functional consequence: Loss of function** (reduced/abolished pejvakin activity — impaired peroxisome proliferation/pexophagy and stereocilia maintenance). The p.C343S mutation directly removes a redox-sensing cysteine required for pexophagy, mechanistically tying genotype to function

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P 30936319

- **Modifier genes:** None validated; *LC3B/MAP1LC3B* is a functional partner whose co-expression enhances rescue (mouse) but is not a human modifier locus

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TRIOBP and *ROCK2*/*IQGAP1* are interactors, not established clinical modifiers

(P 28209736). P 28089576

- **Epigenetics / chromosomal abnormalities:** No disease-specific methylation/histone changes or structural/cytogenetic abnormalities reported; DFNB59 is a single-gene point-mutation/indel disorder (not detected by karyotype/CMA).

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5. Environmental Information

- **Environmental factors: Noise/sound overexposure** is the key environmental modifier (not a primary cause): it drives oxidative stress that the pejvakin-deficient cochlea cannot counter
  (P 26544938). P 30936319
  Ototoxic drugs (aminoglycosides, cisplatin) and aging would plausibly aggravate the oxidative-stress-vulnerable cochlea (inferred).
- **Lifestyle factors:** Avoidance of loud-noise exposure is advisable given sound hypervulnerability (inferred clinical recommendation from mechanism).
- **Infectious agents: Not applicable** — DFNB59 is genetic, not infectious.

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6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Biallelic *PJVK* loss-of-function variant → leads to** absent/non-functional pejvakin in cochlear hair cells and afferent auditory neurons
   (P 16804542 ; demonstrated).
2. Loss of pejvakin → **results in** two converging deficits (branch point):

3. **Branch A (metabolic/antioxidant):** failure of the redox-activated **pexophagy receptor** function (pejvakin normally binds LC3B via an LC3-interacting region in its chaperone domain, using ROS-sensing cysteines C328/C343) → **impairs** sound/oxidative-stress-induced **peroxisome proliferation and turnover** (P 26544938; P 30936319 demonstrated in mouse/in vitro).
4. **Branch B (structural):** loss of pejvakin at the **stereociliary rootlet** (where it binds TRIOBP) → **disrupts** hair-bundle architecture and **mechanoelectrical transduction** (missing shorter-row stereocilia, overextended tips) before hearing onset (P 28209736 demonstrated in mouse).
5. (Branch A) Sound exposure → **triggers** ROS production that is **no longer buffered** by peroxisomes → **causes marked oxidative stress** in hair cells and auditory neurons (P 26544938 demonstrated).
6. Oxidative stress + transduction defect → **leads to** progressive **outer hair cell dysfunction and degeneration**, delayed inner hair cell loss, and auditory-neuron dysfunction (P 28089576; P 28209736 demonstrated in mouse).
7. Hair-cell/neuronal damage along the cochlea and afferent pathway → **produces** the clinical phenotype of **cochlear sensorineural hearing loss and/or auditory neuropathy (abnormal ABR)** (P 16804542 human + mouse).
8. The **degree of acoustic exposure modulates** severity (genotype × environment), explaining intra- and inter-familial variability

(P 26544938 ; inferred link to human variability).

Detail by category

- **Molecular pathways/processes:** peroxisome biogenesis & proliferation (**GO:0016559 peroxisome fission**, **GO:0007031 peroxisome organization**), **selective autophagy/pexophagy** (**GO:0000425 pexophagy**, **GO:0016236 macroautophagy**), **response to oxidative stress** (**GO:0006979**), **Rho/ROCK2 signaling** and actin dynamics via IQGAP1 (**GO:0007266**), stereocilium/hair-bundle maintenance (**GO:0032420 stereocilium**, **GO:0060117**). Partners: **MAP1LC3B/LC3B**, **TRIOBP**, **ROCK2**, **IQGAP1** (P 30936319 P 28209736). P 28089576
- **Protein dysfunction:** loss-of-function; gasdermin-family redox-sensing pexophagy receptor/adaptor activity lost; pathogenic missense (e.g., p.C343S) ablate the ROS-sensing cysteine; mutations disrupt TRIOBP co-localization at rootlets (P 30936319). P 28209736
- **Metabolic/biochemical:** failure of adaptive peroxisomal antioxidant defense; ROS accumulation (CHEBI:26523 reactive oxygen species; CHEBI:16240 hydrogen peroxide).
- **Tissue damage mechanism: oxidative stress** → hair-cell and neuron damage/degeneration (P 26544938).
- **Immune involvement:** none (not autoimmune/inflammatory).
- **Cell types (CL):** cochlear outer hair cell (**CL:0000601**), inner hair cell (**CL:0000589**), spiral ganglion neuron (**CL:0000119**/auditory afferent).
- **Subcellular (GO CC): peroxisome (GO:0005777)**, **autophagosome (GO:0005776)**, **stereocilium/stereocilium rootlet**, nucleus (pejvakin also detected in neuron nuclei,

human)
(P 23407324).

7. Anatomical Structures Affected

- **Organ level: Inner ear / cochlea** (primary). Body system: **auditory (special sensory) nervous system**. Afferent auditory pathway: cochlea → spiral ganglion → cochlear nuclei → superior olivary complex → inferior colliculus (pejvakin expressed throughout in mouse)
(P 23407324). P 16804542
No secondary organ involvement (nonsyndromic).
- **Tissue/cell level:** sensory neuroepithelium of the **organ of Corti — outer hair cells (CL:0000601)** and **inner hair cells (CL:0000589)**; **spiral ganglion neurons (CL:0000119)** (type 1 and type 2 in human)
(P 23407324). P 28089576
In human cochlea, pejvakin labeling was in spiral ganglion neuron cell bodies/nuclei, not in organ-of-Corti structures or stria vascularis
(P 23407324).
- **Subcellular:** peroxisome (**GO:0005777**), autophagosome, stereociliary rootlet; also nucleus (human SGN).
- **Localization (UBERON): cochlea (UBERON:0001844)**, **organ of Corti (UBERON:0002227)**, **spiral ganglion (UBERON:0001691)**, **inner ear (UBERON:0001846)**, **cochlear nucleus (UBERON:0002830)**, **inferior colliculus (UBERON:0001643)**.
- **Lateralization: Bilateral**, generally symmetric (HP:0008619 bilateral SNHL).

8. Temporal Development

- **Onset:** Usually **congenital/prelingual** (childhood); some alleles give **progressive** post-lingual worsening
(P 22617256).
Onset pattern: chronic/insidious.
- **Progression: Variable and allele-dependent** — stable severe-to-profound in some
(P 35052489)
vs slowly progressive with OHC degeneration in others
(P 22617256).
P 28089576
Course is chronic/lifelong; non-episodic, non-relapsing.
- **Critical period:** The **onset of hearing and subsequent sound exposure** is the key vulnerability window — peroxisome structural abnormalities in Pjvk−/− hair cells appear *after* hearing onset, and sound hypervulnerability unfolds thereafter
(P 26544938).
This also defines the **therapeutic window** for early amplification/implantation and (prospectively) gene therapy.
- **Remission:** No spontaneous remission; "functional recovery" is achieved only via device-based rehabilitation (hearing aids/cochlear implants).

9. Inheritance and Population

- **Inheritance: Autosomal recessive** (biallelic). Carriers (heterozygotes) are asymptomatic. Consistent with gnomAD LoF-tolerance (pLI≈0)
(P 16804542).
- **Penetrance/expressivity:** High/complete penetrance for biallelic LoF; **variable expressivity** (severity, progression, cochlear vs neural phenotype), partly driven by acoustic environment

(P 26544938). P 35052489

- **Anticipation / mosaicism:** Not reported / not applicable (no repeat expansion).
- **Founder effects & consanguinity:** Strong association with **consanguinity**; recurrent/ founder alleles in Middle Eastern (Iranian) populations (P 39107234). P 30582396 Original families were Iranian/Moroccan (P 16804542).
- **Carrier frequency:** Not precisely established; individual pathogenic alleles are extremely rare in gnomAD.
- **Epidemiology: Rare**; a **minor cause** of ARNSHL — **~1%** in an Iranian GJB2-negative cohort (P 30582396), **~1.5%** (1/65 families) in a Chinese cohort (P 25631766); among contributing genes in eastern Iran exome studies (P 39107234). No population prevalence/incidence rate established (template "not available").
- **Demographics:** Enriched in consanguineous populations (Middle East, South/East Asia, North Africa, and consanguineous European families). **Sex ratio ~1:1** (autosomal). Age distribution: affected from early childhood (prelingual onset).

10. Diagnostics

- **Audiologic/electrophysiologic (core):** Pure-tone/behavioral audiometry (bilateral SNHL); **otoacoustic emissions (OAE)** and **cochlear microphonics (CM)** — typically **preserved** in ANSD; **auditory brainstem response (ABR)** — **absent/abnormal** in ANSD (key distinguishing test)

(P 16804542). P 27177047

LOINC: audiometry/ABR panels.

- **Imaging:** Temporal-bone CT/MRI usually normal (used to exclude cochlear malformations/ other causes); no DFNB59-specific imaging biomarker.
- **Biopsy/pathology:** Not applicable clinically (inner ear inaccessible); histopathology from mouse models shows OHC degeneration and peroxisome abnormalities (P 28089576). P 26544938
- **Biomarkers:** No circulating biomarker; the molecular "biomarker" is the biallelic *PJVK* genotype. (Oxidative-stress markers are mechanistic, not diagnostic.)
- **Genetic testing (definitive):**
- **NGS hearing-loss gene panels** (include *PJVK*/DFNB59) — first-line after GJB2/GJB6 screening (P 30582396). P 39107234
- **Whole-exome sequencing (WES)** — high yield (~70% in prelingual Iranian cohort) and standard for GJB2-negative/consanguineous cases (P 39107234).
- **WGS** — useful when WES/panel negative; **single-gene *PJVK* sequencing** appropriate when ANSD + OTOF-negative or in families with known allele (P 35052489).
- Methods validated: Sanger, ARMS-PCR, targeted NGS, autozygosity mapping/linkage (consanguineous families).
- CMA/karyotype/FISH/mtDNA/repeat testing: **not applicable** (point mutations/indels).
- **Clinical criteria / differential diagnosis:** Diagnosis = SNHL/ANSD + biallelic pathogenic *PJVK* variants. **Key differentials: OTOF/DFNB9** (the major ANSD gene; exclude first — done in

), P 35052489 GJB2/DFNB1 (most common ARNSHL), other ANSD loci (DIAPH3/AUNA1, AUNX1), and syndromic ANSD. Distinguish via gene testing and syndrome features (P 27177047). P 35052489

- **Screening:** Detected by **newborn hearing screening** (OAE/automated ABR; note ANSD may pass OAE-only screens, so ABR-based screening is important); **carrier/cascade testing** in families with known variants.

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11. Outcome / Prognosis

- **Survival/mortality: Normal life expectancy; no mortality** — DFNB59 is nonsyndromic sensorineural deafness without systemic disease.
- **Morbidity/disability:** Chief morbidity is **permanent hearing disability** affecting communication, language, and education if untreated. ICF domains: communication, hearing functions.
- **Disease course/complications:** Chronic, lifelong; may be stable or progressive. Complications are those of untreated deafness (speech-language delay, educational/social impact).
- **Recovery potential:** No spontaneous recovery; functional hearing restored by **hearing aids or cochlear implantation**, with **good reported outcomes** after unilateral CI (P 35052489).
- **Prognostic factors:** Lesion site (cochlear vs retrocochlear/neural) predicts device efficacy — cochlear-type and residual neuronal function favor better CI outcomes; delineating the site helps predict therapeutic success (P 28209736). Early intervention, degree of residual hearing, and acoustic-exposure history are prognostic (inferred).

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12. Treatment

No disease-specific pharmacotherapy is approved. Management is rehabilitative/device-based; molecular therapies are preclinical.

- **Supportive/rehabilitative (standard of care):**
- **Hearing aids** (NCIT: hearing aid device) for milder/cochlear cases.
- **Cochlear implantation (NCIT:C99359 Cochlear Implant)** — effective; unilateral CI gave "apparent good outcomes" in DFNB59 patients (P 35052489).
  CI candidacy is informed by whether the lesion is cochlear vs neural (P 28209736).
- **Speech-language therapy, auditory-verbal therapy, educational support** (NCIT: rehabilitation therapy).
- **Pharmacotherapy / pharmacogenomics:** None established. Antioxidant strategies are a mechanistic rationale (given oxidative-stress pathophysiology) but **unproven** in DFNB59 (inferred from P 26544938).
- **Advanced/experimental (preclinical, model organism):**
- **AAV gene therapy** — in vivo transduction of Pjvk−/− hair cells with ***Pjvk*** + ***Lc3b*** **cDNAs completely restored sound-induced pexophagy and prevented oxidative stress** (co-delivery outperformed *Pjvk* alone) (P 30936319).
  NCIT:C15431 Gene Therapy. No human trials yet (no NCT identifier for DFNB59 gene therapy at time of writing).
- CRISPR/base-editing, RNA therapies: conceptually applicable; **not yet reported** for *PJVK*.
- **Behavioral/prophylactic: Avoid loud-noise exposure** given sound hypervulnerability (mechanistically motivated) (P 26544938).

- **Treatment strategy:** Genotype/lesion-site-guided — early amplification; CI for severe-to-profound cases; genetic counseling; (future) molecular therapy within the post-hearing-onset critical window.

13. Prevention

- **Primary prevention:** Not preventable at the genetic level. **Noise avoidance / hearing protection** is a rational secondary-prevention measure to limit oxidative-stress-driven progression (inferred from mechanism, P 26544938).
- **Secondary prevention / early detection: Newborn hearing screening** (prefer ABR-based to detect ANSD, which can pass OAE-only screens) and early audiologic diagnosis enable timely amplification/CI.
- **Tertiary prevention:** Early device fitting and rehabilitation to prevent language/educational disability.
- **Genetic screening & counseling: Carrier testing and cascade screening** in families with known variants; **prenatal diagnosis / preimplantation genetic testing (PGT)** available for families with identified biallelic variants; counseling on **25% recurrence risk** and consanguinity (NSGC/ACMG framework, GeneReviews-style).
- **Immunization / public health / environmental:** Not applicable (non-infectious); public-health relevance is premarital/consanguinity genetic counseling in high-prevalence regions.

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** *Pjvk* is conserved in vertebrates. Mouse ***Pjvk*** (NCBI Gene; **Mus musculus**, NCBI:txid10090); orthologs in rat (**Rattus norvegicus**, txid10116) and other mammals; the C343 residue is fully conserved across vertebrate orthologs (P 22617256). Zebrafish (txid7955) gasdermin/pejvakin-like orthology exists but is not a primary disease model here.

- **Natural disease in animals: No naturally occurring *PJVK* deafness** documented in companion animals/livestock in OMIA (not applicable); all animal data are from engineered models.
- **Comparative biology:** Mouse models recapitulate human sound-hypervulnerability, OHC degeneration, abnormal ABR, and peroxisome defects, indicating **evolutionarily conserved mechanism** (P 26544938). P 28089576
  Zoonotic/cross-species transmission: **not applicable** (genetic disease).

15. Model Organisms

- **Mouse (primary model, *Mus musculus*, NCBI:txid10090):**
- ***Pjvk*−/− knockout** — variable auditory phenotype, sound hypervulnerability, cochlear oxidative stress, impaired peroxisome proliferation and pexophagy, post-hearing-onset peroxisome structural abnormalities (P 26544938). P 30936319
  Recapitulates the oxidative-stress mechanism.
- **R183W knock-in** (first model) — abnormal ABR indicating neuronal (auditory-pathway) dysfunction (P 16804542).
- **G292R (c.874G>A) knock-in** — generated to study auditory **and vestibular** phenotypes of DFNB59 (P 32917362).
- **"sirtaki"** — C-terminal deletion mutant; IHC ribbon-synapse transmission largely preserved, supporting a primary OHC role (P 28089576).

- **Conditional (floxed) *Pjvk*** — deletion in all hair cells or only OHCs → early-onset profound loss; adult OHC deletion → slowly progressive loss with OHC then IHC degeneration (demonstrates cell-autonomous OHC requirement) (P 28089576).
- **In vitro / cellular:** injectoporated hair cells (TRIOBP colocalization) (P 28209736); transfected cell lines for LC3B-binding and cysteine-mutagenesis assays (P 30936319).
- **Phenotype recapitulation:** Strong for cochlear/OHC pathology, sound vulnerability, and peroxisome/pexophagy biology. **Limitations:** phenotypic variability/inconsistency across *Pjvk* alleles complicates modeling; mouse data suggest hair-cell-autonomous disease whereas human expression and some phenotypes emphasize **neuronal** involvement — an unresolved species/allele difference (P 32917362 P 28209736 P 23407324).
- **Resources:** MGI (mouse *Pjvk*), IMPC/IMSR for alleles; published strains from Institut Pasteur (Petit/Delmaghani lab), Rutgers (Schwander lab), and NTU (Wu lab).

Key Findings Summary (with statistical/evidentiary support)

1. Biallelic ***PJVK* LoF** causes DFNB59, variable cochlear vs ANSD phenotype (P 16804542 P 28089576 P 22617256).

2. Pejvakin is a **peroxisome-associated antioxidant protein**; its loss → oxidative stress and **sound hypervulnerability** (P 26544938).
3. Pejvakin is a **redox-activated pexophagy receptor** (LC3B binding; C328/C343 ROS sensors); **AAV *Pjvk+Lc3b*** rescues the defect in mice (P 30936319).
4. **Cell-autonomous OHC role** via TRIOBP/stereociliary rootlet and ROCK2/IQGAP1; progressive OHC→IHC degeneration (P 28209736, P 28089576).
5. Expression across **hair cells and the entire afferent auditory pathway** explains cochlear + neural phenotypes (P 23407324).
6. **Rare**, consanguinity-enriched, **minor** ARNSHL cause (~1–1.5% of cohorts) with LoF-tolerant gnomAD constraint (P 30582396, P 25631766, P 39107234).
7. **Cochlear implantation** gives good outcomes; lesion-site delineation guides therapy (P 35052489, P 28209736).

Supported vs Refuted Hypotheses

- **Supported:** PJVK loss → impaired peroxisome antioxidant defense → sound-triggered oxidative damage → hair-cell/neuron injury → hearing loss; cell-autonomous OHC role; AAV gene-therapy rescue (mouse); recessive LoF genetics.

- **Refuted/qualified:** "Pejvakin acts purely as a neuronal protein" — mouse data show a hair-cell-autonomous (non-neuronal-essential) requirement (P 28209736), qualifying the original neuronal-only model (P 16804542).

Limitations & Future Directions

- No literature-derived precise prevalence/incidence, carrier frequency, or human QoL metrics for DFNB59 specifically.
- Genotype–phenotype correlation is limited by few reported cases (P 35052489).
- Species/allele discrepancy (neuronal vs hair-cell-autonomous) remains unresolved.
- Human translation of AAV gene therapy and antioxidant/noise-protection strategies is untested.

Evidence source types: human clinical/genetic (P 16804542, P 22617256, P 25631766, P 30582396, P 35052489, P 39107234, P 23407324, P 27177047),

mouse model organism
(
P *26544938*
P *28089576*
P *30936319*
),
P *32917362*
in vitro
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P *28209736*
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P *30936319*
computational/population (gnomAD).
