Autosomal Recessive Nonsyndromic Hearing Loss 77 (DFNB77): A Comprehensive Disease Characterization

Disease: Autosomal Recessive Nonsyndromic Hearing Loss 77 (DFNB77) **MONDO ID:** MONDO:0013119 · **OMIM:** #613079 · **Category:** Mendelian (autosomal recessive) **Causal gene:** *LOXHD1* (OMIM 613072; HGNC:26521; NCBI Gene 125336; 18q21.1) **Report type:** Aggregated disease-level synthesis from primary literature and public databases (no individual-patient/EHR data used)

Summary

Autosomal Recessive Nonsyndromic Hearing Loss 77 (DFNB77; OMIM #613079; MONDO:0013119) is a rare Mendelian sensorineural hearing loss caused by **biallelic (homozygous or compound-heterozygous) loss-of-function or destabilizing missense variants in *LOXHD1***, a gene on chromosome 18q21.1 encoding "lipoxygenase homology PLAT domains 1." The LOXHD1 protein is composed almost entirely of 15 tandem **PLAT (polycystin/lipoxygenase/alpha-toxin) domains** and localizes along the membrane of mature cochlear hair-cell stereocilia. DFNB77 was first defined through the ENU-induced *samba* mouse and subsequently confirmed in human deafness families (PMID: 19732867).

Mechanistically, DFNB77 is a disease of **failed mechanotransduction rather than failed hair-bundle development.** In *Loxhd1* mutant mice, stereocilia and tip links form normally and tip-link complex proteins (Harmonin, LHFPL5) remain correctly localized, yet mechanotransduction (MET) currents — near-normal in the first postnatal week — collapse by postnatal day 11, after which hair cells progressively degenerate (PMID: 33707295; PMID: 19732867). This post-developmental functional failure explains the characteristic human phenotype: **early-onset but progressive, bilateral, often high-frequency sensorineural hearing loss of highly variable severity, with preserved vestibular function** and no syndromic features (PMID: 31547530; PMID: 29676012).

DFNB77 shows extensive **allelic heterogeneity** (missense, nonsense, frameshift, and splice-site variants distributed across the PLAT repeats), **population-specific founder alleles** (e.g., the Japanese splice variant c.4212+1G>A), and **variable expressivity without a clear genotype–phenotype correlation.** Population-genetic analysis of gnomAD confirms *LOXHD1* is loss-of-function tolerant (LOEUF ≈ 0.93; pLI ≈ 0), the expected signature of a recessive gene requiring two hits, with a broadly pan-ancestry predicted-loss-of-function carrier frequency of ~0.3–0.7%. There is **no gene-specific therapy**; management is standard sensorineural hearing-loss care — hearing aids and cochlear implantation, the latter effective in severe-to-profound cases (PMID: 42131115).

Key Findings

F001 — DFNB77 is caused by biallelic *LOXHD1* mutations encoding a PLAT-domain stereociliary protein

DFNB77 (OMIM #613079) is caused by **biallelic loss-of-function and destabilizing missense variants in *LOXHD1*** (gene OMIM 613072; NCBI Gene 125336; HGNC:26521), located on chromosome **18q21.1**. The protein "lipoxygenase homology PLAT domains 1" is architecturally distinctive: it is built almost entirely from **15 PLAT (polycystin/lipoxygenase/alpha-toxin) repeats**, a domain class associated with lipid-membrane binding. LOXHD1 localizes along the membrane of mature cochlear hair-cell stereocilia. The gene was discovered through the ENU-induced *samba* mouse model and then confirmed as the cause of human DFNB77 (Grillet et al., 2009).

> *"LOXHD1 consists entirely of PLAT (polycystin/lipoxygenase/alpha-toxin) domains and is expressed along the membrane of mature hair cell stereocilia."* — PMID: 19732867
>
> *"we screened DNA from human families segregating deafness and identified a mutation in LOXHD1, which causes DFNB77, a progressive form of autosomal-recessive nonsyndromic hearing loss (ARNSHL)"* — PMID: 19732867

Ontology anchors: gene product — LOXHD1 (UniProt R4GN98); UBERON:0002227 (cochlea); CL:0000855 (sensory hair cell); GO:0032420 (stereocilium); MONDO:0013119.

F002 — Mechanism: LOXHD1 loss causes a post-developmental mechanotransduction defect, then hair-cell degeneration

The central mechanistic insight is that DFNB77 is **not a developmental hair-bundle malformation** but a **failure to activate an otherwise intact mechanotransduction apparatus.** In two independent *Loxhd1* mouse models carrying mutations in the 10th PLAT repeat, MET currents in inner hair cells (IHCs) were near wild-type during the first postnatal week but became severely reduced by postnatal day 11 (Trouillet et al., 2021, *J Neurosci*). Critically, this defect was **not** attributable to abnormal hair-bundle morphology or a reduction in tip-link number, and the tip-link complex proteins **Harmonin and LHFPL5 remained properly localized** — indicating the MET machinery is present but not activatable. In the original *samba* mouse, stereociliary development was likewise unaffected, but hair-cell function was perturbed and hair cells eventually degenerated, providing the cellular basis for the progressive clinical course.

> *"While mechanotransduction currents in mutant inner hair cells (IHCs) were similar to wild-type levels in the first postnatal week, they were severely affected by postnatal day 11."* — PMID: 33707295
>
> *"two proteins of the upper and lower TL protein complexes (Harmonin and LHFPL5) were maintained in the mutants, suggesting that the mechanotransduction machinery was present but not activatable"* — PMID: 33707295
>
> *"Stereociliary development is unaffected in samba mice, but hair cell function is perturbed and hair cells eventually degenerate."* — PMID: 19732867

Ontology anchors: GO:0050910 (detection of mechanical stimulus involved in sensory perception of sound); GO:0060088 (auditory receptor cell stereocilium organization); GO:0007605 (sensory perception of sound); CL:0000589 (cochlear inner hair cell); CL:0000601 (cochlear outer hair cell).

F003 — Phenotype: progressive, mostly early-onset bilateral sensorineural hearing loss, variable severity, no vestibular dysfunction

Across cohorts, DFNB77 presents as **bilateral sensorineural hearing loss with early onset in most patients but variable progression rates, variable severity, and no vestibular involvement.** In the largest reported cohort (8,074 Japanese hearing-loss patients; Maekawa et al., 2019), 28 affected individuals carried *LOXHD1* variants; these patients mostly showed

early-onset hearing loss with differing progression rates, and no accompanying symptoms — including vestibular dysfunction — were detected. A Dutch series of 9 DFNB77 families (Wesdorp et al., 2018) documented high inter- and intrafamilial variation in the hearing phenotype. Minami et al. (2016) described milder, predominantly high-frequency loss in compound heterozygotes carrying a truncating + missense genotype, with a progressive course. In the founding description, DFNB77 was defined as one of only three genes (with *MYO3A* and *PJVK/DFNB59*) linked to **progressive** ARNSHL.

> *"Patients with LOXHD1 variations mostly showed early onset hearing loss and presented different progression rates."* — PMID: 31547530
>
> *"No accompanying symptoms, including vestibular dysfunction, with hearing loss were detected in this study."* — PMID: 31547530
>
> *"These cases showed less severe hearing impairment than the previously reported cases carrying LOXHD1 mutations, but their hearing loss appeared to be progressive."* — PMID: 26973026

Suggested HPO terms:

HPO term	Label	Notes
HP:0000407	Sensorineural hearing impairment	Core phenotype
HP:0008527	Congenital sensorineural hearing impairment	Early/congenital-onset subset
HP:0000408	Progressive sensorineural hearing impairment	Progressive course
HP:0008550	High-frequency hearing impairment	High-frequency predominance in some genotypes
HP:0000365	Hearing impairment	General
HP:0000359	Abnormality of the inner ear	Cochlear localization

Normal vestibular function argues **against** vestibular-dysfunction terms.

F004 — Genetics/epidemiology: allelic heterogeneity with population-specific founder alleles; a minor but recurrent ARNSHL gene

The *LOXHD1* mutation spectrum spans **missense, nonsense, frameshift, and splice-site** variants distributed across the PLAT repeats. A recurrent splice variant, **c.4212+1G>A**, is a **Japanese founder allele** detected in 18 of 28 *LOXHD1* patients (Maekawa et al., 2019); haplotype analysis suggested a mutational hot spot with multiple ancestral origins. *LOXHD1* recurs as a cause of ARNSHL across diverse populations: a Chinese NSHL cohort (Zhang et al., 2026: 10 variants, 5 novel, among 157 probands), consanguineous Arab-Israeli families (Danial-Farran et al., 2018), a Turkish ARNSHL panel (Atik et al., 2015), and Dutch families (Wesdorp et al., 2018: 15 variants, 12 novel, across 9 families). Consanguinity increases homozygous risk, consistent with a recessive mechanism.

> *"we identified ten different variants in the LOXHD1 gene from five patients in their families"* — PMID: 42131115
>
> *"deafness was explained by damaging alleles of SLC26A4, MYO15A, OTOG, LOXHD1, and TBC1D24"* — PMID: 30139988

F005 — Management and the disputed LOXHD1–Fuchs corneal dystrophy association

There is **no gene-specific therapy**; management follows the standard of care for sensorineural hearing loss — **hearing aids and cochlear implantation (CI)**. Two Chinese DFNB77 patients with severe bilateral SNHL showed significant improvement after cochlear implantation, attaining age-appropriate receptive and expressive language (Zhang et al., 2026). Separately, heterozygous *LOXHD1* missense variants have been reported in late-onset **Fuchs endothelial corneal dystrophy (FECD)**, but a systematic ACMG-based reassessment concluded that the causal role of *LOXHD1* (along with *SLC4A11*, *ZEB1*, *AGBL1*) in FECD is **not established**; targeted screening of DFNB77 carriers did not support a link.

> *"two patients with severe bilateral sensorineural hearing loss associated with LOXHD1 mutations showed significant improvement after cochlear implantation, attaining receptive and expressive language skills appropriate for their chronological age"* — PMID: 42131115

> *"The causal role of other genes, SLC4A11, ZEB1, LOXHD1, and AGBL1, which have been reported to be associated with FECD, is more complicated and less obvious."* — PMID: 37441688

Suggested NCIT terms: Cochlear Implant (NCIT:C50076); Hearing Aid (NCIT:C50113); Genetic Counseling (NCIT:C15681).

F006 — Variable expressivity without clear genotype–phenotype correlation; diagnosis by NGS panels/exome

The Dutch series of 9 DFNB77 families (15 variants) found **high inter- and intrafamilial variation** in severity and progression, with **no clear correlation between variant type/location and phenotype**, leading the authors to hypothesize contributions from environmental factors or genetic modifiers. That study also found no vestibular involvement and no FCD in heterozygous carriers. Minami et al. (2016) showed a truncating + missense compound-heterozygous genotype produced milder high-frequency loss, and SWISS-MODEL predicted that the p.V1892F PLAT-domain mutant reduces lipid-membrane affinity — a plausible molecular explanation for hair-cell dysfunction. Diagnosis is molecular: **targeted next-generation sequencing deafness panels, whole-exome/whole-genome sequencing**, with Sanger confirmation and family segregation. Audiometric evaluation (pure-tone/ORCA audiometry) characterizes the sensorineural, often high-frequency, progressive loss.

> *"The hearing phenotype showed high inter- and intrafamilial variation in severity and progression."* — PMID: 29676012
>
> *"a clear correlation between the type or location of the variant and the severity or progression of HI could not be established"* — PMID: 29676012
>
> *"No association was found between heterozygous LOXHD1 variants and the occurrence of FCD in carriers."* — PMID: 29676012
>
> *"distorted structure of the PLAT domain in the p.V1892F mutant could lead to decreased affinity of the protein to lipid membrane resulting in hair cell dysfunction"* — PMID: 26973026

F007 — gnomAD constraint and ClinVar burden confirm *LOXHD1* as a recessive, LoF-tolerant deafness gene

gnomAD v2/v4 constraint metrics for *LOXHD1* (ENSG00000167210; ENST00000642948) show **pLI ≈ 0** (1.8e-56) and an observed/expected loss-of-function ratio **oe_lof** = **0.826** (90% CI 0.737–0.927; LOEUF ≈ 0.93), with lof_z = 2.33 and mis_z = 0.33. This signature indicates *LOXHD1* is **not haploinsufficient** / **not LoF-intolerant** — heterozygous loss-of-function is tolerated in the general population, exactly as expected for an autosomal-recessive disease gene where two hits are required to produce disease. ClinVar lists ~3,112 submitted *LOXHD1* variants; several hundred (~634 by text match) are classified pathogenic/likely pathogenic, reflecting extensive allelic heterogeneity, while the large majority of the remainder are variants of uncertain significance (VUS).

Constraint metric	Value	Interpretation
pLI	≈ 0 (1.8e-56)	Not haploinsufficient
oe_lof (LOEUF)	0.826 (90% CI 0.737–0.927) ≈ 0.93	LoF-tolerant
lof_z	2.33	Mild LoF constraint only
mis_z	0.33	Missense unconstrained
ClinVar P/LP	~634 of ~3,112	Extensive allelic heterogeneity

F008 — gnomAD-derived estimate: pLoF carrier frequency ~0.5%, predicted biallelic-LoF prevalence ~6.5 per million (lower bound)

A computational estimate from gnomAD v4 identified **474 predicted-LoF variants** in *LOXHD1* (471 LOFTEE high-confidence). The summed pLoF allele frequency **q ≈ 0.00255 (0.25%)**. Under Hardy–Weinberg equilibrium, the carrier frequency $2q(1-q) \approx$ **0.51% (~1 in 197)**, and the predicted biallelic (homozygous + compound-heterozygous) LoF birth prevalence $q^2 \approx$ **6.5×10^{-6} (~1 in 154,000)**. This is a **loss-of-function-only lower bound**: it excludes pathogenic missense and in-frame alleles (which constitute a large share of reported DFNB77 alleles, e.g., p.V1892F), so the true DFNB77 prevalence is expected to be several-fold higher. The estimate also assumes complete penetrance, panmixia (thereby underestimating burden in consanguineous populations), and correct LOFTEE annotation.

F009 — LOXHD1 LoF carrier burden is broadly pan-ancestry, highest in Ashkenazi Jewish and European groups

Ancestry-resolved aggregation of LOFTEE high-confidence pLoF alleles in gnomAD v4 shows carrier burden is **broadly similar across major ancestries (within ~2-fold)**, slightly higher in Ashkenazi Jewish and European populations:

Ancestry	Carrier freq 2q(1−q)	~1 in N
Ashkenazi Jewish (q≈0.0035)	~0.70%	~143
Admixed American	~0.56%	~180
African / African-American	~0.56%	~180
Non-Finnish European (AN>1M)	~0.55%	~182
East Asian	~0.47%	~215
Finnish	~0.42%	~238
South Asian	~0.39%	~256
Middle Eastern (AN≈5,700)	~0.32%	~313
Amish (AN≈912)	0	—

Full Section-by-Section Report

1. Disease Information

DFNB77 is a rare, autosomal-recessive, nonsyndromic **sensorineural hearing loss** caused by biallelic *LOXHD1* variants. **Identifiers:** OMIM #613079 (phenotype); gene OMIM 613072; MONDO:0013119; MeSH — indexed under "Deafness"/"Hearing Loss, Sensorineural"; ICD-10 H90.3 (bilateral sensorineural hearing loss) / ICD-11 AB52; Orphanet — nonsyndromic genetic deafness umbrella (ORPHA:90636). **Synonyms:** DFNB77; deafness, autosomal recessive 77; *LOXHD1*-related nonsyndromic hearing loss. **Information source:** aggregated disease-level and family-based clinical genetics data (OMIM, cohort studies), not EHR-derived.

2. Etiology

Causal factor: monogenic — biallelic pathogenic *LOXHD1* variants. **Genetic risk factors:** homozygous or compound-heterozygous *LOXHD1* alleles (missense, nonsense, frameshift, splice-site); **consanguinity** raises homozygous risk (F004). No established modifier genes, though variable expressivity implies possible modifiers/environment (F006). **Environmental risk factors:** none specific to DFNB77; general acquired-hearing-loss factors (noise, ototoxic drugs, aging) may compound but are not causal. **Protective factors:** none identified. **Gene–environment interactions:** hypothesized but unproven; Wesdorp et al. invoked environmental factors/modifiers to explain phenotypic variability absent a genotype correlation (PMID: 29676012).

3. Phenotypes

Core phenotype: **bilateral sensorineural hearing loss** (clinical sign / audiometric laboratory abnormality). **Onset:** mostly early-onset/childhood, occasionally congenital; **severity:** mild to profound, variable; **progression:** progressive in most, at variable rates; **frequency among affected:** hearing loss is obligate (100%), with high-frequency predominance in some genotypes. **No vestibular dysfunction** and **no syndromic features** (F003). **Quality-of-life impact:** communication, language acquisition, and educational/social functioning are affected, as expected for bilateral SNHL; cochlear implantation restores age-appropriate language in severe cases (F005). HPO terms per F003 (HP:0000407, HP:0000408, HP:0008527, HP:0008550).

4. Genetic/Molecular Information

Causal gene: *LOXHD1* (18q21.1; HGNC:26521; NCBI Gene 125336; gene OMIM 613072). **Variant classes:** missense, nonsense, frameshift, splice-site — distributed across the 15 PLAT repeats (F004). **Notable alleles:** c.4212+1G>A (Japanese founder splice variant, 18/28 patients); p.V1892F (PLAT-domain missense predicted to reduce lipid-membrane affinity) (F004, F006). **Classification:** ACMG/AMP pathogenic/likely pathogenic for established alleles; ~634/3,112 ClinVar entries P/LP, remainder largely VUS (F007). **Allele frequency:** individual pathogenic alleles rare; summed pLoF q ≈ 0.25% (F008). **Origin:** germline. **Functional consequence:** loss of function / destabilization → failure of MET activation (F002). **Constraint:** LoF-tolerant (LOEUF ≈ 0.93; pLI ≈ 0), consistent with recessive biology (F007). **Modifier genes / epigenetics / chromosomal abnormalities:** none established.

5. Environmental Information

No environmental, lifestyle, or infectious agents are established as causes of DFNB77. General ototoxic exposures (aminoglycosides, cisplatin, noise) and aging are non-specific aggravators of any sensorineural hearing loss but are not part of DFNB77 etiology.

6. Mechanism / Pathophysiology

Ordered causal chain:

1. **Biallelic *LOXHD1* loss-of-function/destabilizing variants** (germline) → reduced or absent functional LOXHD1 PLAT-domain protein at the stereociliary membrane. *(demonstrated — F001)*
2. Loss of LOXHD1 → stereocilia and tip links still **form and mature normally**; MET complex proteins (Harmonin, LHFPL5) remain localized. *(demonstrated — F002)*
3. However, the assembled MET machinery **cannot be activated** → mechanotransduction currents collapse after the first postnatal week (by ~P11 in mouse). *(demonstrated — F002; molecular link to lipid-membrane binding inferred from p.V1892F modeling — F006)*
4. Loss of MET current → **hair-cell functional failure** → deprivation of normal receptor-current activity. *(demonstrated)*
5. Chronic dysfunction → **progressive hair-cell degeneration** (over time). *(demonstrated in mouse; inferred as substrate of human progression — F002/F003)*
6. Hair-cell loss → **progressive bilateral sensorineural hearing loss**, high-frequency predominant, variable severity, vestibular sparing. *(clinical — F003)*

```
LOXHD1 biallelic LoF/missense
        │
        ▼
Normal stereocilia + tip links form (Harmonin, LHFPL5 present)
        │
        ▼
MET channel present but NOT activatable  ← p.V1892F ↓ lipid-membrane affinity (inferred)
        │
        ▼
MET current collapses post-development (~P11 mouse)
        │
        ▼
Hair-cell functional failure ⟶ progressive hair-cell degeneration
        │
        ▼
Progressive bilateral SNHL (variable severity, high-freq, vestibular-sparing)
```

Upstream vs downstream: the mutation and MET-activation failure are upstream; hair-cell degeneration and clinical hearing loss are downstream. **Cell types:** cochlear inner hair cells (CL:0000589) and outer hair cells (CL:0000601). **Biological processes (GO):** GO:0050910, GO:0007605, GO:0060088. **Subcellular:** stereocilium membrane (GO:0032420 stereocilium; GO:0016020 membrane). **Metabolic/immune/omics profiling:** not applicable — DFNB77 is a structural/functional hair-cell disorder, not metabolic or immune-mediated.

7. Anatomical Structures Affected

Organ: cochlea / inner ear (UBERON:0002227 cochlea; UBERON:0001846 internal ear); body system — auditory/special sense. **Secondary organ involvement:** none (nonsyndromic; vestibular apparatus spared). **Tissue/cell:** cochlear sensory epithelium (organ of Corti); **cochlear hair cells** — inner (CL:0000589) and outer (CL:0000601). **Subcellular:** stereocilia / stereociliary membrane (GO:0032420). **Localization:** bilateral; cochlear.

8. Temporal Development

Onset: mostly early-onset/childhood, sometimes congenital; insidious. **Progression:** typically **progressive** at variable rates; some milder high-frequency forms (F003). **Course:** chronic, lifelong, non-remitting. **Critical period:** the post-developmental window (analogous to mouse ~P11) marks the transition from functional to degenerative loss — a conceptual window for intervention before hair-cell death.

9. Inheritance and Population

Inheritance: autosomal recessive; **penetrance:** high/complete for biallelic pathogenic genotypes (assumed); **expressivity:** variable, without clear genotype–phenotype correlation (F006). **No anticipation** (not a repeat disorder). **Founder effects:** Japanese c.4212+1G>A (F004). **Consanguinity:** increases homozygous risk. **Carrier frequency (pLoF only):** ~0.5% overall; pan-ancestry ~0.3–0.7%, highest in Ashkenazi Jewish (~0.70%) and European (~0.55%) groups (F008, F009). **Predicted biallelic-LoF prevalence:** ~1 in 154,000 (lower bound; true prevalence higher once missense alleles counted). **Sex ratio:** ~1:1. *LOXHD1* is a **minor but recurrent** contributor to ARNSHL across populations.

10. Diagnostics

Audiology: pure-tone audiometry (and ORCA/specialized audiometry) documents bilateral, often high-frequency, progressive SNHL; OAE/ABR for objective testing. **Genetic testing is definitive:** targeted **NGS hearing-loss gene panels**, **whole-exome (WES)** and **whole-genome (WGS)** sequencing, with **Sanger confirmation and family segregation** (F004, F006). Single-gene testing is low-yield given ARNSHL locus heterogeneity; panels/exome preferred. CMA/karyotype/FISH/mtDNA/repeat testing are **not applicable** (point/indel variants). **Differential diagnosis:** other ARNSHL genes (*GJB2*, *SLC26A4*, *MYO15A*, *OTOF*, *TMC1*, *CDH23*, *OTOG*, *MYO7A*) and syndromic causes (Usher, Pendred), distinguished by the absence of vestibular/retinal/thyroid features in DFNB77. **Screening:** carrier and cascade testing in families; newborn hearing screening detects the phenotype non-specifically.

11. Outcome/Prognosis

Survival/mortality: DFNB77 is **not life-limiting**; normal life expectancy. **Morbidity:** hearing-related disability affecting communication, language, and education. **Course:** progressive hearing loss; **recovery:** no spontaneous recovery, but functional restoration is achievable with amplification and cochlear implantation (F005). **Prognostic factors:** severity/progression are variable and not well predicted by genotype (F006); earlier intervention improves language outcomes.

12. Treatment

No gene-specific or pharmacological therapy exists. Management is standard sensorineural hearing-loss care: **hearing aids** for mild-to-moderate loss and **cochlear implantation** for severe-to-profound loss, with documented restoration of age-appropriate language in DFNB77 CI recipients (PMID: 42131115). **Rehabilitative:** auditory-verbal/speech therapy, educational

support. **Experimental/advanced:** no *LOXHD1*-specific gene therapy or clinical trials identified; the large multi-PLAT transcript makes conventional AAV gene replacement technically challenging (cargo-size limit). **Pharmacogenomics/combination/personalized regimens:** not applicable. **NCIT terms:** Cochlear Implant (NCIT:C50076); Hearing Aid (NCIT:C50113); Speech Therapy (NCIT:C15315).

13. Prevention

Primary prevention: not possible for a monogenic disease; **genetic counseling** informs reproductive decisions. **Secondary:** newborn/early hearing screening enables early amplification/implantation; **carrier and cascade screening** in at-risk families and consanguineous couples; **prenatal/preimplantation genetic testing** available when familial variants are known. **Tertiary:** prevent language/communication deficits via timely audiologic intervention. No immunization or environmental prevention applies.

14. Other Species / Natural Disease

Taxonomy: studied in *Mus musculus* (NCBI Taxon 10090). **Orthologous gene:** mouse *Loxhd1* (NCBI Gene 240873). **Natural disease:** no well-characterized naturally occurring DFNB77-equivalent reported in companion animals in the reviewed literature; the mouse models are induced (ENU / targeted). **Comparative biology:** LOXHD1 is an evolutionarily conserved stereociliary protein (PMID: 19732867); the mechanotransduction pathway is conserved across vertebrate hair cells. **Zoonotic/transmission:** not applicable.

15. Model Organisms

Mouse (*Mus musculus, mammalian):* the ENU-induced* samba *allele (Grillet et al., 2009) and two additional* Loxhd1* mutant lines with 10th-PLAT-repeat mutations (Trouillet et al., 2021). Model types: **ENU-induced point mutants and targeted alleles.** Phenotype recapitulation — high: **models reproduce normal stereociliary development, post-developmental MET-current failure, progressive hair-cell degeneration, and progressive hearing loss, faithfully mirroring the human disease mechanism (F002).** Limitations: **mouse progression timescale differs; the highly variable human expressivity and putative modifiers are not captured; specific human missense alleles (e.g., p.V1892F) modeled computationally rather than in vivo.** Applications: **dissecting MET-channel activation, tip-link complex biology, and timing of hair-cell degeneration.** Resources: *MGI (Loxhd1)*, IMPC.

Mechanistic Model / Interpretation

DFNB77 is best understood as a **"machinery present but not activatable" mechanotransduction disorder.** This distinguishes it from deafness genes whose loss disrupts hair-bundle architecture or tip-link assembly. LOXHD1, a membrane-associated 15-PLAT-domain protein, appears required not to *build* the transduction apparatus but to *maintain its activatable state* after development. The convergent evidence — normal early MET currents that collapse by P11, intact Harmonin/LHFPL5 localization, preserved bundle morphology, and a missense allele (p.V1892F) predicted to weaken lipid-membrane binding — points to LOXHD1 supporting the lipid/membrane environment or mechanical coupling needed for sustained channel gating. The downstream degeneration is a secondary consequence of chronic functional deprivation and is the substrate of the **progressive** clinical course. The recessive, LoF-tolerant population-genetic signature (LOEUF ≈ 0.93; pLI ≈ 0) is exactly what this two-hit disease biology predicts.

Feature	DFNB77 (LOXHD1)	Interpretation
Bundle development	Normal	Not a morphogenesis defect
Tip links / MET proteins	Present (Harmonin, LHFPL5)	Machinery assembled
MET current	Normal early → collapses ~P11	Post-developmental activation failure
Hair cells over time	Progressive degeneration	Basis of clinical progression
Vestibular function	Spared	Cochlea-selective phenotype
Constraint (gnomAD)	LoF-tolerant, pLI≈0	Consistent with recessive inheritance

Evidence Base

PMID	Title (abbrev.)	Role
19732867	*Mutations in LOXHD1… disrupt hair cell function… progressive hearing loss*	**Foundational** — gene discovery, PLAT/ stereocilia localization, samba mouse, DFNB77 definition
33707295	Trouillet et al., *J Neurosci* (Loxhd1 MET function)	**Core mechanism** — post-developmental MET collapse; machinery present but not activatable
31547530	*Mutational Spectrum and Clinical Features* (Maekawa, Japan)	**Phenotype/epidemiology** — 28 patients, early onset, no vestibular signs, c.4212+1G>A founder
29676012	Wesdorp et al. (9 Dutch families)	**Expressivity** — variable phenotype, no genotype correlation, no FCD in carriers
26973026	Minami et al. (Japanese family, compound het)	**Genotype–phenotype** — milder high-freq loss; p.V1892F reduces lipid affinity
42131115	Zhang et al. (Chinese cohort)	**Management** — 10 variants; cochlear implant restores age-appropriate language
30139988	Danial-Farran et al. (consanguineous Arab families)	**Recurrence** — LOXHD1 among recessive deafness alleles
26561413	Atik et al. (Turkish ARNSHL panel)	**Recurrence/diagnostics** — NGS panel detection of LOXHD1
37441688	Systematic review — SLC4A11/ZEB1/ LOXHD1/AGBL1 in FECD	**Refutes/qualifies** the LOXHD1–Fuchs corneal dystrophy association

gnomAD/ClinVar (computational): constraint and allele-frequency analyses (F007–F009) were derived from gnomAD v2/v4 and ClinVar, supporting recessive, LoF-tolerant biology and pan-ancestry carrier estimates.

Limitations and Knowledge Gaps

- **Prevalence is a lower bound.** The ~1 in 154,000 figure counts only predicted-LoF alleles; pathogenic missense/in-frame variants (a large share of real DFNB77 alleles) are excluded, so true prevalence is likely several-fold higher. Estimates also assume complete penetrance and panmixia, underestimating burden under consanguinity.
- **Precise molecular function of LOXHD1 is unresolved.** Whether it stabilizes the MET channel's lipid environment, contributes to mechanical coupling, or has another role is inferred, not proven; the p.V1892F lipid-affinity effect is computational (SWISS-MODEL).
- **No genotype–phenotype correlation** and unexplained variable expressivity; modifier genes and environmental contributors are hypothesized but unidentified.
- **The LOXHD1–FECD link remains unresolved** and is not supported for DFNB77 carriers.
- **No systematic human natural-history study** quantifies progression rate or per-frequency audiometric trajectories.
- **No disease-specific therapeutics or trials**; gene-therapy feasibility is limited by the large transcript.

Proposed Follow-up Experiments / Actions

1. **Refine prevalence:** aggregate ClinVar P/LP + curated pathogenic missense allele frequencies in gnomAD (not just LOFTEE pLoF) to produce a missense-inclusive, ancestry-stratified prevalence estimate.
2. **Mechanistic biophysics:** test whether LOXHD1 PLAT domains bind specific stereociliary phospholipids (e.g., PIP2) in vitro, and whether p.V1892F and other PLAT missense alleles reduce binding — connecting F006's computational prediction to function.
3. **Timing/rescue in mouse:** determine whether AAV- or conditional re-expression of *Loxhd1* before ~P11 preserves MET currents and prevents hair-cell degeneration, defining the therapeutic window (Section 8 critical period).
4. **Natural-history registry:** compile serial audiograms across DFNB77 patients to quantify progression rate and identify audiometric predictors, addressing the expressivity gap (F006).
5. **Modifier search:** in the well-phenotyped Dutch/Japanese cohorts, test candidate modifier loci and environmental exposures against progression rate.

6. **Definitively resolve the FECD association** via large ACMG-based case-control cohorts, since current evidence (F005/F006) argues against a role for *LOXHD1* heterozygosity in Fuchs dystrophy.

Report compiled from 9 confirmed findings and 11 reviewed papers across a 5-iteration autonomous investigation. Evidence sources span human clinical genetics (cohort and family studies), mouse model-organism data, in vitro/structural modeling, and computational population genetics (gnomAD/ClinVar).
