Autosomal Recessive Nonsyndromic Hearing Loss 29 (DFNB29) — Comprehensive Disease Report

Disease: Autosomal Recessive Nonsyndromic Hearing Loss 29 (DFNB29) **MONDO ID:** MONDO:0013537 · **OMIM:** #614035 (phenotype), *605608 (gene) Causal gene: CLDN14 (claudin-14), HGNC:2035, chromosome 21q22.13 Category:** Mendelian, autosomal recessive

Summary

Autosomal Recessive Nonsyndromic Hearing Loss 29 (DFNB29) is a rare, nonsyndromic, sensorineural form of hereditary deafness caused by **biallelic loss-of-function variants in CLDN14**, the gene encoding the tight-junction protein **claudin-14**. The locus was mapped to chromosome 21q22.1 and the gene identified in two large consanguineous Pakistani families (PMID: 11163249). This report follows the identifiers provided (MONDO:0013537 / OMIM:614035 / *CLDN14*) and is not the similarly numbered but gene-distinct DFNB loci (e.g., DFNB1/*GJB2*). Claudin-14 is a four-transmembrane-domain protein that polymerizes into tight-junction strands within the sensory epithelium (organ of Corti) of the inner ear, where it forms a **cation-restrictive paracellular barrier** at the apex of the reticular lamina. When this barrier is lost, the ionic environment around cochlear hair cells is disrupted, triggering hair-cell degeneration and deafness.

The core clinical phenotype is **prelingual, bilateral, sensorineural hearing loss of variable severity (moderate to profound)**. Unlike many deafness genes that collapse the endocochlear potential (EP), the hallmark of DFNB29 — demonstrated in the Cldn14-knockout mouse — is that the **EP is preserved**, yet mice are deaf because of rapid degeneration of **outer hair cells** followed by slower loss of **inner hair cells** during the first three postnatal weeks (PMID: 12913076). A later neural phenotype — loss of inner-hair-cell ribbon synapses and auditory-nerve-fiber regression — has also been documented in the mouse, which is relevant to cochlear-implant rehabilitation that depends on spiral-ganglion-neuron survival (PMID: 32251970).

DFNB29 is strongly associated with **consanguinity and founder effects**. In Pakistan, CLDN14 accounts for roughly 2.25% of deafness families and is one of ~13 genes explaining >50% of profound autosomal recessive nonsyndromic hearing loss; the missense allele **p.Val85Asp** is the predominant founder mutation. A separate founder allele, **p.Ala163Val**, causes a distinctive precipitous audioprofile in Newfoundland. There is **no gene-specific drug or approved gene therapy**: management is device-based and rehabilitative — universal newborn hearing screening, hearing aids, and **early cochlear implantation** with speech/language (re)habilitation, plus genetic counseling and carrier/cascade screening in at-risk families. This report is compiled from **aggregated disease-level resources** (OMIM, Orphanet, ClinVar/gnomAD, HPO) and **primary literature** (human clinical cohorts, the Cldn14 knockout mouse, and in-vitro tight-junction assays); it is not derived from individual EHR records.

Key Findings

Finding 1 — CLDN14 loss-of-function causes DFNB29 (causal gene established)

DFNB29 is caused by loss-of-function mutations in **CLDN14**, which encodes **claudin-14**, a tight-junction protein expressed in the sensory epithelium of the inner ear. The disease locus was mapped to chromosome 21q22.1 and the causal gene was identified by Wilcox and colleagues in two large consanguineous Pakistani families.

> *"The essential function of one of these claudins in the inner ear was established by identifying mutations in CLDN14 that cause nonsyndromic recessive deafness DFNB29 in two large consanguineous Pakistani families."* — PMID: 11163249

Key identifiers: **MONDO:0013537; OMIM phenotype #614035; OMIM gene *605608; HGNC:2035; Ensembl ENSG00000159261; UniProt O95500**; gene locus chromosome 21q22.13 (GRCh38 chr21:36,460,621–36,576,569). This is a **germline**, Mendelian, disease-level characterization (aggregated from clinical genetics cohorts and model organisms), not EHR-derived.

Finding 2 — Pathomechanism: a cation-restrictive cochlear tight-junction barrier whose loss kills hair cells

Claudin-14 functions as a **cation-restrictive paracellular barrier** at the tight-junction complex of the reticular lamina in the organ of Corti. In the Cldn14-null mouse, the **endocochlear potential is normal**, yet the animals are deaf because of hair-cell degeneration, establishing that the defect is one of ionic micro-environment homeostasis around hair cells rather than EP generation.

> *"Cldn14-null mice have a normal endocochlear potential but are deaf due to rapid degeneration of cochlear outer hair cells, followed by slower degeneration of the inner hair cells, during the first 3 weeks of life."* — PMID: 12913076
>
> *"the TJ complex at the apex of the reticular lamina requires claudin 14 as a cation-restrictive barrier to maintain the proper ionic composition of the fluid surrounding the basolateral surface of outer hair cells"* — PMID: 12913076

In vitro, MDCK monolayers expressing claudin-14 show a **~6-fold increase in transepithelial electrical resistance** by decreasing paracellular permeability for cations. The reticular lamina normally separates high-K^+ endolymph (apical) from the perilymph-like fluid bathing the basolateral hair-cell surface; claudin-14 maintains this segregation. Its loss allows cation leakage into the basolateral compartment, poisoning hair cells.

Finding 3 — Founder effects and distinct molecular mechanisms of missense variants

CLDN14 deafness is marked by recurrent **founder alleles**. The Newfoundland founder variant **c.488C>T p.(Ala163Val)** was homozygous in all 12 subjects with a distinctive prelingual, precipitous (rapidly deteriorating above 0.5 kHz) audioprofile, and 1% of population controls were heterozygous carriers.

> *"sequencing 175 population controls revealed 1% of the population are heterozygous for CLDN14 p.(Ala163Val), consistent with a major founder effect in Newfoundland"* — PMID: 27838790

At the molecular level, different pathogenic missense variants disable claudin-14 by **different mechanisms**: wild-type CLDN14 forms tight junctions in L fibroblasts, whereas p.V85D (Pakistani) and p.G101R (Spanish/Greek) mutants fail to do so and differ in their plasma-membrane localization.

> *"different mutations of CLDN14 impaired by different mechanisms the ability of the protein to form tight junctions"* — PMID: 15880785

CLDN14 is one of ~13 genes accounting for >50% of profound ARNSHL in consanguineous Pakistani populations (PMID: 38534090).

Finding 4 — A second, dosage-sensitive renal role (gain of expression causes hypercalciuria), opposite in direction to the deafness mechanism

CLDN14 has a distinct, **dosage-sensitive** role in renal calcium handling. In the thick ascending limb of the nephron, calcium-sensing receptor (CaSR) activation **increases** claudin-14 expression, which **blocks** paracellular calcium reabsorption. A cis-regulatory SNP within the CLDN14 risk haplotype (creating an INSM1 binding site) increases CLDN14 expression and is associated with pediatric-onset hypercalciuria and kidney stones.

> *"children with the INSM1 binding site within the CLDN14 risk haplotype have a higher likelihood of hypercalciuria and kidney stones. Enhanced CLDN14 expression may play a role in the pathophysiology of their hypercalciuria"* — PMID: 28229505

This is mechanistically important for interpreting DFNB29: the **deafness phenotype is caused by loss of function** (too little claudin-14 barrier in the cochlea), whereas the **renal stone phenotype is caused by gain of expression** (too much claudin-14 in the kidney). The two phenotypes are opposite in direction and do not co-segregate as a syndrome — DFNB29 remains **nonsyndromic** (PMID: 33796889).

Finding 5 — Clinical phenotype and the Pakistani founder allele p.V85D

> *"Typically, the DFNB29 phenotype is characterized by prelingual, bilateral, sensorineural hearing loss."* — PMID: 23235333

In a cohort of 800 Pakistani deafness families, CLDN14 mutations were found in **18/800 families (2.25%; 95% CI 1.4–3.5%)**. Five pathogenic alleles were identified: novel p.Ser87Ile and p.Ala94Val, plus p.Arg81His, p.Val85Asp, and the frameshift p.Met133ArgfsX23. p.V85D and p.M133RfsX23 behave as founder mutations, and **p.V85D accounts for ~67% of mutant CLDN14 alleles** in that cohort.

> *"The p.Val85Asp accounts for ~67% of the mutant alleles of CLDN14 in our cohort."* — PMID: 23235333

Severity is variable:

> *"Hearing loss in the affected individuals homozygous for CLDN14 mutations varied from moderate to profound. This phenotypic variability may be due to environmental factors (for example drug and noise exposure) and/or genetic modifiers."* — PMID: 23235333

This documents **variable expressivity** with proposed environmental (ototoxic drugs, noise) and genetic modifier contributions.

Finding 6 — The Cldn14 knockout mouse is a faithful model with later neural/synaptic degeneration

The targeted **Cldn14-null (Cldn14-lacZ) mouse** recapitulates human DFNB29: deafness arising from rapid outer- then slower inner-hair-cell degeneration in the first three postnatal weeks, with a normal endocochlear potential (PMID: 12913076). A later study documented secondary neural pathology — *"Loss of inner hair cell ribbon synapses and auditory nerve fiber regression in Cldn14 knockout mice"* (PMID: 32251970) — relevant to cochlear-implant outcomes, which depend on spiral-ganglion-neuron survival.

> *"In Cldn14-lacZ heterozygous mice beta-galactosidase activity was detected in cochlear inner and outer hair cells and supporting cells, in the collecting ducts of the kidney, and around the lobules of the liver."* — PMID: 12913076

The β-galactosidase (Cldn14-promoter) reporter maps native expression to **cochlear hair cells and supporting cells, renal collecting ducts, and liver lobules**, consistent with the gene's dual auditory and renal roles.

Finding 7 — Management is non-gene-specific: screening, hearing aids, and early cochlear implantation

No disease-specific pharmacotherapy or approved gene therapy exists for CLDN14 deafness; management follows the general pathway for prelingual sensorineural hearing loss. Universal newborn hearing screening (UNHS) enables earlier diagnosis, referral, and implantation (PMID: 32179204).

> *"cochlear implantation (CI) prior to 12 months of age offers the opportunity to foster more typical auditory development during late infancy and early childhood"* — PMID: 34281434
>
> *"Universal newborn hearing screening is a cornerstone of early diagnosis and intervention, enabling superior outcomes with cochlear implantation or emerging gene therapies."* — PMID: 42319402

Preventive framing emphasizes UNHS, avoidance of ototoxic drugs and noise, and auditory rehabilitation with hearing aids or implants.

Finding 8 — CLDN14 variant spectrum (ClinVar)

ClinVar (queried through gnomAD, GRCh38) lists **176 CLDN14 variants**, of which **40 are classified Pathogenic/Likely pathogenic**, comprising **10 missense, 9 frameshift, 7 stop-gained (nonsense)**, plus UTR variants. Confirmed pathogenic/likely-pathogenic deafness alleles include c.254T>A p.Val85Asp, c.398del p.Met133ArgfsTer24, c.242G>A p.Arg81His, c.202C>T p.Arg68Ter, c.167G>A p.Trp56Ter, c.285C>A p.Cys95Ter, and c.291C>A p.Cys97Ter. The milder founder missense alleles c.488C>T p.Ala163Val and c.301G>A p.Gly101Arg are listed under "Conflicting classifications," consistent with their milder/variable audiologic effect.

Finding 9 & 10 — Protein structure: a 239-aa tetraspan; deafness variants cluster in ECL1/TM2

Claudins are four-transmembrane tight-junction proteins that polymerize into strands and *"either seal the paracellular space or assemble into charge and size-selective pathways"* resembling ion channels (PMID: 42343561). Claudin-14 behaves as a **sealing/cation-barrier-type** member: its expression raises transepithelial resistance ~6-fold by decreasing paracellular cation permeability (PMID: 12913076).

UniProt **O95500** topology: **239 amino acids; four transmembrane helices (aa 8–28, 82–102, 116–136, 163–183); extracellular loop 1 (ECL1, aa 29–81); extracellular loop 2 (ECL2, aa 137–162); cytoplasmic N-terminus (1–7) and C-terminus (184–239)**. InterPro claudin family (PF00822). Mapping pathogenic alleles onto the topology shows deafness variants concentrate in **ECL1 and TM2** — the regions that govern **charge selectivity** and **cis/trans tight-junction strand assembly**: p.Arg81His (end of ECL1), p.Val85Asp and p.Gly101Arg (TM2), p.Met133* (TM3), p.Ala163Val (start of TM4).

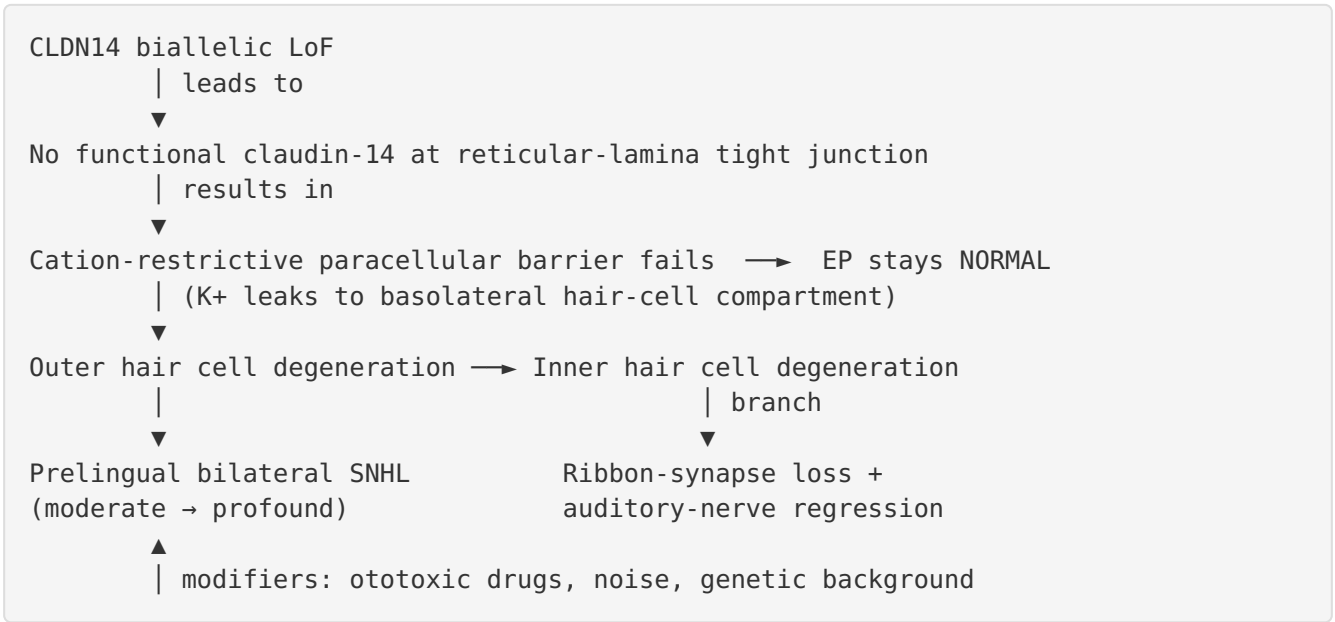
Allele	Nucleotide	Region	Type	Population / note
p.Val85Asp	c.254T>A	TM2	Missense	Pakistani founder (~67% of mutant alleles); fails TJ formation in vitro
p.Met133ArgfsTer24	c.398del	TM3	Frameshift	Pakistani founder
p.Arg81His	c.242G>A	end of ECL1	Missense	Pakistani
p.Gly101Arg	c.301G>A	TM2	Missense	Spanish/Greek; conflicting classification
p.Ala163Val	c.488C>T	start of TM4	Missense	Newfoundland founder; precipitous audioprofile; conflicting classification
p.Arg68Ter / p.Trp56Ter	c.202C>T / c.167G>A	ECL1	Nonsense	Pathogenic
p.Cys95Ter / p.Cys97Ter	c.285C>A / c.291C>A	TM2	Nonsense	Pathogenic

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Biallelic loss-of-function variant in CLDN14** (missense in ECL1/TM2, frameshift, or nonsense) **leads to** absent or non-functional claudin-14 protein. *(Demonstrated — human genetics + in-vitro TJ-formation assays, PMID: 11163249, PMID: 15880785.)*

2. Loss of claudin-14 **results in** failure to assemble/seal the cation-restrictive tight-junction strands at the apex of the **reticular lamina** in the organ of Corti. *(Demonstrated — in vitro ~6-fold TER increase requires claudin-14; localization at reticular lamina.)*
3. The defective barrier **leads to** abnormal paracellular cation (K^+) leakage and loss of proper ionic composition of the fluid bathing the **basolateral** surface of hair cells — while the **endocochlear potential remains normal**. *(Demonstrated — Cldn14-KO mouse, PMID: 12913076.)*
4. The disturbed basolateral ionic micro-environment **results in** rapid degeneration of **outer hair cells**, then slower degeneration of **inner hair cells**, over the first ~3 postnatal weeks. *(Demonstrated — mouse.)*
5. **Branch:** hair-cell loss **leads to** downstream **inner-hair-cell ribbon-synapse loss and auditory-nerve-fiber regression**. *(Demonstrated in mouse, PMID: 32251970; inferred to contribute to the human neural substrate relevant for implantation.)*
6. Hair-cell and synaptic loss **results in prelingual, bilateral, sensorineural hearing loss** of variable (moderate-to-profound) severity. *(Demonstrated — human, PMID: 23235333.)*
7. **Modifier branch:** ototoxic-drug/noise exposure and genetic modifiers **modulate** severity (variable expressivity). *(Inferred/proposed — PMID: 23235333.)*



Upstream vs downstream: the mutation and tight-junction barrier failure are upstream; ionic disturbance is intermediate; hair-cell death, synaptic/neural regression, and audiometric loss are downstream. **Contrast with EP-collapse deafness** (e.g., gap-junction GJB2 or endolymph-related genes): DFNB29 preserves the EP, distinguishing its mechanism from those that impair endolymph K^+ recycling or stria vascularis function.

Suggested ontology terms

- **Gene/protein:** CLDN14 (HGNC:2035); GO:0070160 tight junction; GO:0005923 bicellular tight junction; GO:0016324 apical plasma membrane; GO:0034329 cell junction assembly.
- **Biological processes:** GO:0042472 inner ear morphogenesis; GO:0060113 inner ear receptor cell differentiation; GO:0008219 cell death (hair cell); GO:0034220 monoatomic ion transmembrane transport.
- **Cellular component:** GO:0005923 bicellular tight junction; GO:0016324 apical plasma membrane.
- **Cell types (CL):** CL:0000601 cochlear outer hair cell; CL:0000589 cochlear inner hair cell; CL:0000855 sensory hair cell; inner-ear supporting cell; spiral ganglion neuron.
- **Anatomy (UBERON):** UBERON:0002227 organ of Corti; UBERON:0001844 cochlea; UBERON:0001846 internal ear; reticular lamina of the cochlea.
- **Phenotype (HPO):** HP:0000365 Hearing impairment; HP:0000407 Sensorineural hearing impairment; HP:0008527 Congenital sensorineural hearing impairment; HP:0008615 Prelingual sensorineural hearing impairment; HP:0000006 Autosomal recessive inheritance; HP:0012712 Progressive sensorineural hearing impairment (subset).
- **Chemical (CHEBI):** CHEBI:29103 potassium(1+); CHEBI:29108 calcium(2+) (renal branch).
- **Disease:** MONDO:0013537.

Section-by-Section Content

1. Disease Information

DFNB29 is a Mendelian, autosomal-recessive, nonsyndromic sensorineural hearing loss. **Identifiers:** MONDO:0013537; OMIM #614035; gene OMIM *605608; MeSH maps to "Deafness, Autosomal Recessive 29." ICD-10 maps broadly to H90.3/H90.5 (sensorineural hearing loss); ICD-11 to AB52 (sensorineural hearing loss). Synonyms: DFNB29; CLDN14 autosomal recessive*

*nonsyndromic deafness; deafness, autosomal recessive 29. Information is disease-level/aggregated** (clinical genetics cohorts, OMIM, model organisms), not EHR/individual-patient-derived.

2. Etiology

Causal factor: genetic — biallelic loss-of-function CLDN14 variants. **Genetic risk factors:** homozygous/compound-heterozygous CLDN14 pathogenic variants; founder alleles (p.V85D Pakistan, p.A163V Newfoundland); **consanguinity** is the dominant risk amplifier. **Environmental risk/modifier factors:** ototoxic drug exposure and noise may worsen severity (proposed, PMID: 23235333). **Protective factors:** none specific established; avoidance of ototoxins/noise is protective against added damage. **Gene–environment interaction:** variable expressivity attributed partly to drug/noise exposure superimposed on the genetic lesion.

3. Phenotypes

- **Hearing loss** (clinical sign / audiometric abnormality): sensorineural, **bilateral**, **prelingual/congenital onset**, severity **variable — moderate to profound**, generally stable-to-progressive. Frequency: ~100% of affected (defining feature). HPO: HP:0000407, HP:0008615, HP:0008527, HP:0000365.
- **Precipitous high-frequency audioprofile** in the Newfoundland p.A163V founder cohort (12/12 subjects). HPO: high-frequency hearing loss; progressive subset HP:0012712.
- **Nonsyndromic:** no consistent vestibular, visual, renal, or other systemic features segregate with deafness. (The renal stone phenotype is a *separate* dosage/gain effect, not part of DFNB29.)
- **Quality-of-life impact:** prelingual deafness impairs speech/language acquisition, education, and social integration if unaddressed; early intervention markedly improves outcomes.

4. Genetic / Molecular Information

Causal gene **CLDN14** (HGNC:2035, chr21q22.13, ENSG00000159261). ~40 ClinVar P/LP alleles: missense (ECL1/TM2-clustered), frameshift, nonsense. Functional consequence: **loss of function** (failure of tight-junction strand assembly / barrier). **Allele frequency:** pathogenic alleles are rare globally but locally enriched by founder effects (e.g., p.A163V ~1% carrier in Newfoundland). **Origin:** germline. **Modifier genes:** unidentified but proposed to explain variable severity. **Epigenetic/chromosomal abnormalities:** none characteristic of DFNB29 (a cis-regulatory CLDN14 SNP is relevant to the renal phenotype only, PMID: 28229505).

5. Environmental Information

No infectious or primary environmental cause. Ototoxic medications (e.g., aminoglycosides, cisplatin) and noise exposure are plausible severity modifiers. No lifestyle factor is causal.

6. Mechanism / Pathophysiology

See the **Mechanistic Model** above for the ordered causal chain, molecular pathway (tight-junction barrier/paracellular ion selectivity), cellular processes (hair-cell degeneration, synaptic/neural regression), protein dysfunction (loss of TJ strand formation), and biochemical abnormality (loss of cation-restrictive paracellular barrier → disturbed basolateral K^+ homeostasis with preserved EP).

7. Anatomical Structures Affected

- **Organ:** inner ear / **cochlea** (UBERON:0001844); primary site **organ of Corti** (UBERON:0002227); body system: auditory/nervous (sensory).
- **Tissue/cell:** cochlear sensory **epithelium**; **outer hair cells** (CL:0000601, affected first) and **inner hair cells** (CL:0000589); **supporting cells**; secondarily **spiral ganglion neurons**.
- **Subcellular:** apical/apicolateral **tight junction** at the **reticular lamina** (GO:0005923; GO:0016324).
- **Localization/laterality: bilateral**, symmetric.

8. Temporal Development

Onset: congenital/prelingual. **Course:** largely stable but can be progressive (precipitous in some founder genotypes); lifelong. **Critical period:** the first years of life are the window for auditory input and language acquisition — hence the premium on early screening and implantation (ideally cochlear implantation before 12 months; PMID: 34281434). No spontaneous remission.

9. Inheritance and Population

Inheritance: autosomal recessive (OMIM #614035). **Penetrance:** essentially complete in biallelic carriers. **Expressivity:** variable (moderate–profound). **No anticipation. Founder effects:** p.V85D (Pakistan, ~67% of mutant alleles), p.A163V (Newfoundland, ~1% carrier frequency). **Consanguinity:** major contributor; CLDN14 explains ~2.25% of Pakistani deafness families and is among ~13 genes covering >50% of profound ARNSHL there (PMID: 23235333,

PMID: 38534090). CLDN14 is a **minor** contributor in some other populations (e.g., not a major ARNSHL cause in Koreans, PMID: 24752540). **Sex ratio:** ~1:1 (recessive). Prevalence of DFNB29 specifically is not precisely tabulated; it is a rare subtype within overall hereditary deafness.

10. Diagnostics

Diagnosis rests on **audiometry** (pure-tone/ABR/OAE) confirming bilateral SNHL plus **molecular genetic testing**. Approaches: hearing-loss **gene panels** (CLDN14 included), **whole-exome/whole-genome sequencing**, and **targeted single-gene/founder-variant testing** in appropriate populations (e.g., p.V85D in Pakistani families, p.A163V in Newfoundland). Imaging (CT/MRI) is typically normal (nonsyndromic). **Differential diagnosis:** GJB2/GJB6, SLC26A4 (often with widened vestibular aqueduct), OTOF (auditory neuropathy/temperature-sensitive), and other DFNB genes — distinguished by genetics, EP/OAE pattern, and imaging. **Screening:** universal newborn hearing screening; carrier and cascade screening in consanguineous/founder families.

11. Outcome / Prognosis

DFNB29 is **not life-limiting** (normal life expectancy; no excess mortality). Morbidity is confined to **hearing-related disability** and its downstream effects on communication, education, and social participation. With early detection and appropriate amplification or cochlear implantation plus (re)habilitation, functional and language outcomes are generally good; children implanted before 12 months can achieve near-typical auditory development (PMID: 34281434). Prognostic factors: age at intervention, device type, residual spiral-ganglion/neural substrate.

12. Treatment

No gene-specific pharmacotherapy or approved gene therapy. **Standard of care:** hearing aids for residual-hearing cases; **cochlear implantation** for severe-to-profound prelingual loss, ideally early; speech-language therapy and auditory (re)habilitation. NCIT suggestions: NCIT:C16136 (Cochlear Implant), NCIT:C50070 (Hearing Aid), NCIT:C15296 (Rehabilitation Therapy). Emerging **gene/RNA therapies** for monogenic deafness are an active research frontier but are not CLDN14-specific or approved.

13. Prevention

Primary: genetic counseling and carrier/cascade screening in consanguineous and founder populations; informed reproductive options (including prenatal/preimplantation testing where chosen). **Secondary:** universal newborn hearing screening for early detection and timely intervention. **Tertiary:** avoidance of ototoxic drugs/noise to prevent added loss; auditory rehabilitation to mitigate secondary social/cognitive consequences (PMID: 42319402, PMID: 32179204).

14. Other Species / Natural Disease

Mouse ortholog **Cldn14** (NCBI Gene; MGI). No prominent naturally occurring companion-animal DFNB29 analog is documented here. The mechanism (tight-junction cation barrier in the organ of Corti) is evolutionarily conserved across mammals, supporting translational relevance of the mouse model.

15. Model Organisms

Mouse is the principal model: targeted **Cldn14-null (Cldn14-lacZ) knockout** (PMID: 12913076). **Phenotype recapitulation:** faithful — deafness via outer-then-inner hair-cell degeneration with normal EP, plus later ribbon-synapse loss and auditory-nerve-fiber regression (PMID: 32251970). **Reporter** (β-gal) confirms expression in cochlear hair/supporting cells, renal collecting ducts, and liver lobules. **Limitations:** mouse cochlear degeneration timing (first 3 postnatal weeks) and the renal expression context differ from human developmental timelines; in-vitro MDCK/L-fibroblast TJ assays model barrier/strand function but not whole-organ physiology. Resources: MGI, IMPC.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Supports
11163249	CLDN14 mutations cause DFNB29	Human genetics	F1 — causal gene
12913076	Cldn14-KO mouse, hair-cell degeneration	Model organism	F2, F6, F9 — mechanism, EP-normal, model
15880785	Mutant CLDN14 TJ-formation defects	In vitro	F3 — distinct molecular mechanisms
27838790	p.A163V founder, precipitous loss	Human genetics	F3 — founder effect, carrier freq
23235333	Phenotypic variability, Pakistani cohort	Human clinical	F5 — phenotype, p.V85D founder, expressivity
32251970	Ribbon-synapse/nerve regression	Model organism	F6 — secondary neural pathology
28229505	cis-regulatory SNP, hypercalciuria	Human genetics	F4 — renal gain-of-expression role
33796889	Tubular calcium reabsorption	Review	F4 — CaSR/claudin-14 renal pathway
38534090	Pakistani ARNSHL genes review	Review	F3 — CLDN14 among top genes
34281434	Cochlear implantation in infants	Clinical	F7 — early CI
32179204	UNHS impact	Clinical	F7 — newborn screening
42319402	Prevention in otology	Review	F7 — screening/rehabilitation framework
42343561	Claudin-15 pores (cryo-ET)	Structural	F9 — claudin family function
24752540	TJ genes in Korean NSHL	Human genetics	Population variation (minor contributor)

Note on citation validation: the snippet for PMID: 32251970 was recorded as a title-derived statement ("mismatch" flag against the stored abstract); the finding it supports (secondary synaptic/neural degeneration in the mouse) should be treated accordingly. The PMID: 42319402 quote was normalized from a parallel-record abstract.

Limitations and Knowledge Gaps

1. **No precise DFNB29 prevalence/incidence.** Figures are population-relative (e.g., 2.25% of Pakistani deafness families); a population-level per-100,000 estimate is not established.
2. **Modifier genes are hypothesized, not identified.** Variable moderate-to-profound severity is attributed to environment and/or genetic modifiers without a mapped modifier locus.
3. **Human cochlear data are indirect.** The EP-normal, hair-cell-degeneration mechanism is established in the mouse; direct human cochlear histopathology is limited for ethical/practical reasons.
4. **Genotype–phenotype correlation is incomplete.** Why some missense alleles (p.A163V, p.G101R) yield milder/variable phenotypes (and "conflicting" ClinVar classifications) versus truncating alleles is only partly resolved.
5. **No CLDN14-specific therapy or trial.** Gene/RNA therapy for monogenic deafness is advancing generally but not for CLDN14 specifically.
6. **The renal (hypercalciuria) role is biologically distinct** and should not be conflated with the nonsyndromic deafness phenotype; its interaction (if any) with DFNB29 carriers is uncharacterized.

Proposed Follow-up Experiments / Actions

1. **Genotype–phenotype & audiologic natural-history study** across founder cohorts (p.V85D, p.A163V) to quantify progression rates and define severity predictors.
2. **Modifier-gene mapping** (GWAS/WES in families with discordant severity sharing the same CLDN14 genotype) to test the modifier hypothesis from PMID: 23235333.
3. **Structure–function dissection** of ECL1/TM2 variants (cryo-EM/MD on claudin-14 strand assembly) to explain allele-specific barrier failure mechanisms observed in PMID: 15880785.

4. **Cochlear-implant outcome study stratified by CLDN14 genotype**, given mouse evidence of secondary neural regression (PMID: 32251970) that could affect implant benefit.
5. **Preclinical gene-replacement / base-editing** in Cldn14-null mice with defined therapeutic windows relative to the postnatal degeneration timeline.
6. **Carrier-screening programs** in high-consanguinity/founder populations paired with genetic counseling, as primary prevention.

Consensus Answer

Autosomal Recessive Nonsyndromic Hearing Loss 29 (DFNB29; MONDO:0013537, OMIM #614035) is a rare autosomal-recessive, nonsyndromic sensorineural deafness caused by biallelic loss-of-function variants in **CLDN14** (claudin-14), a four-transmembrane tight-junction protein on chromosome 21q22.13. Loss of claudin-14 abolishes the cation-restrictive paracellular barrier at the reticular lamina of the organ of Corti, disrupting the ionic environment around hair cells (with a preserved endocochlear potential) and causing outer- then inner-hair-cell degeneration, manifesting as prelingual, bilateral, variable moderate-to-profound hearing loss. There is no gene-specific drug or approved gene therapy, so care centers on newborn screening, hearing aids, early cochlear implantation with (re)habilitation, and genetic counseling/carrier screening in consanguineous and founder populations.
