MOLECULAR ATLAS · VARIANT CARD

WFS1 R708L — Wolframin

Arginine → Leucine at position 708 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic, auditory neuropathy. AlphaMissense 0.954, DynaMut2 ΔΔG +0.20 kcal/mol — STABILISING. A charge-loss variant where the fold tightens slightly.

IDENTITY

Variant	R708L (p.Arginine708Leucine)
DNA change	c.2123G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002683858
Amino acid change	Arginine (R) → Leucine (L) — large positively-charged guanidinium replaced by branched hydrophobic. Loss of charge entirely.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 708	**93.44** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 708 in the ER lumen (pLDDT 93).
IDR flag	No — pLDDT well above 50 threshold

Position 708 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places R708 within 5 Å of VAL709 (2.4 Å), VAL707 (2.5 Å — same V707 as V707F Atlas card), and GLU776 (3.8 Å — likely salt-bridge partner). The wild-type arginine likely forms an intramolecular salt bridge with E776 across the lumenal fold. Replacing R708 with leucine eliminates that salt bridge entirely. The DynaMut2 ΔΔG of +0.20 (stabilising) reflects that the leucine packs more efficiently into the hydrophobic V707-V709 local environment than the long arginine side chain did. AlphaMissense's 0.954 + auditory neuropathy clinical evidence confirm severe functional consequence. The mechanism is loss of the R708-E776 salt bridge that the wild-type fold relied on, even though the local packing improves.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.954	**0.2** kcal/mol	**93.44**
am_class: **LPath** — threshold > 0.564	Stabilising · Job 177991929911	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2023/12/22 00:00
Inheritance	Auditory neuropathy documented.
WFS1 variant landscape	R708L is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Auditory neuropathy

RESEARCH PATH DECISION TREE

```
ΔΔG < 2 + binding site affected → CATEGORY 3 — docking experiments ΔΔG 2–4 → CATEGORY 2 — pharmacological chaperones ΔΔG > 4 → CATEGORY 1 — gene therapy pLDDT < 50 → CATEGORY 5 — IDR, experimental only Stable fold + functional site hit → CATEGORY 4 — site-specific docking
```

Category 4 — Stable Fold, Function Disrupted. ΔΔG = +0.20 stabilising. AlphaMissense 0.954 + auditory neuropathy confirm severe functional consequence.

Mechanism is loss of R708-E776 salt bridge. Therapeutic strategy: bridge restoration through site-directed small molecules at the E776 microregion. Combined with V707F (adjacent position), drug discovery has convergent targets.

R708L is another Atlas stabilising-but-pathogenic variant. Combined with V707F at the adjacent position, the 707-708 microregion has two convergent therapeutic targets.