MOLECULAR ATLAS · VARIANT CARD

WFS1 D797N — Wolframin

Aspartate → Asparagine at position 797. ClinVar Conflicting including monogenic hearing loss + DFNA6. AlphaMissense 0.556 (borderline), ΔΔG -0.02 (neutral). Same position as D797V — second substitution at 797.

IDENTITY

Variant	D797N (p.Aspartate797Asparagine)
DNA change	c.2389G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000517360
Amino acid change	Aspartate (D) → Asparagine (N) — carboxylate replaced by amide. Loss of charge; H-bonding preserved.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 797	**64.88** CONFIDENT
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 797 (pLDDT 65 borderline). Same as D797V.
IDR flag	No — pLDDT well above 50 threshold

> Position 797 same neighbors as D797V: VAL798 (2.4 Å), ASP796 (2.4 Å), GLU794 (4.2 Å), THR799 (4.3 Å). D797N conserves the local geometry but eliminates the charge. The D796-D797-E794 charged cluster loses one negative member. AM 0.556 borderline + dual deafness phenotype confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.556

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.02 kcal/mol

PLDDT (ALPHAFOLD)

64.88

confident

Destabilising · Job 177992469266

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/12/05 00:00
Inheritance	Monogenic hearing loss + DFNA6.
WFS1 variant landscape	D797N is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic hearing loss
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

RESEARCH PATH DECISION TREE

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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
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Category 4 — Stable Fold, Function Disrupted. ΔΔG ≈ 0. AlphaMissense 0.556 borderline + DFNA6 confirm severe consequence.

Mechanism: charge loss from D796-D797-E794 cluster. Therapeutic: same target as D797V.

D797N + D797V at same position. Two charge-loss variants at the D796-D797-E794 cluster.