MOLECULAR ATLAS · VARIANT CARD

WFS1 N714T — Wolframin

Asparagine → Threonine at position 714 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic, associated with rare genetic deafness. AlphaMissense 0.927, DynaMut2 ΔΔG -0.23 kcal/mol (destabilising). A conservative polar-to-polar substitution with subtle but consequential mechanism.

IDENTITY

Variant	N714T (p.Asparagine714Threonine)
DNA change	c.2141A>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000045447
Amino acid change	Asparagine (N) → Threonine (T) — a polar amide-bearing residue replaced by a polar hydroxyl-bearing residue. Both are small polar, but H-bonding chemistry differs: asparagine has an amide donor/acceptor pair, threonine has a single hydroxyl donor/acceptor.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 714	**87.12** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 714 in the ER lumen (pLDDT 87).
IDR flag	No — pLDDT well above 50 threshold

Position 714 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places N714 within 5 Å of SER715 (2.4 Å), ASP713 (2.5 Å — likely H-bond partner), PHE770 (4.4 Å, long-range), ALA716 (4.4 Å), and ASP771 (4.7 Å, long-range). The local environment is unusual — two adjacent aspartates in spatial proximity (D713 immediately upstream, D771 across the fold), suggesting N714 sits in a polar interaction network. The wild-type asparagine's amide carries both H-bond donor (NH2) and acceptor (C=O) capacity. The wild-type N714 likely engages D713 and possibly D771 across the fold through this dual H-bond chemistry. Replacing asparagine with threonine swaps the amide for a hydroxyl. Threonine's hydroxyl has H-bond donor AND acceptor capacity through the same oxygen, but the geometry

differs from asparagine's amide. The H-bond network to D713/D771 reorganizes; some contacts may be preserved, others lost. The |ΔΔG| of 0.23 is small — the fold barely registers the swap. But AlphaMissense's 0.927 score and the clinical evidence (rare genetic deafness) confirm functional consequence. The mechanism is likely subtle reorganization of the local H-bond network that perturbs partner-protein recognition geometry.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.927	**-0.23** kcal/mol	**87.12**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990266041	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2013/08/15 00:00
Inheritance	Documented in association with rare genetic deafness. AD-leaning presentation pattern.
WFS1 variant landscape	N714T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Rare genetic deafness

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 3/4 — Most Druggable. |ΔΔG| = 0.23 kcal/mol — fold barely perturbed. AlphaMissense 0.927 confirms pathogenic functional consequence.

The mechanism is reorganization of the H-bond network involving D713 (immediate neighbor) and D771 (longer-range). Therapeutic strategy: site-directed small molecules at the D713-N714-D771 network. The pathogenic mechanism is fine-grained H-bond geometry rather than gross structural disruption.

N714T is a conservative substitution whose pathogenicity is invisible to crude analysis but clear to AlphaMissense and clinical evidence. The Atlas captures the specific H-bond network involving two distant aspartates (D713 and D771) that the wild-type asparagine maintained — a structural feature that fine-grained drug discovery can target.
