MOLECULAR ATLAS · VARIANT CARD

WFS1 N714S — Wolframin

Asparagine → Serine at position 714 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic for DFNA6 hearing loss. AlphaMissense 0.640 (just above threshold), DynaMut2 ΔΔG -0.49 kcal/mol (destabilising). Third Atlas variant at position 714 (with N714T, N714K).

IDENTITY

Variant	N714S (p.Asparagine714Serine)
DNA change	c.2141A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003387796
Amino acid change	Asparagine (N) → Serine (S) — polar amide replaced by polar hydroxyl. Both H-bond capable but different geometry.

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). Same position as N714T and N714K.
IDR flag	No — pLDDT well above 50 threshold

Position 714 same neighbor environment as N714T and N714K: SER715 (2.4 Å), ASP713 (2.5 Å), PHE770 (4.4 Å), ALA716 (4.4 Å), ASP771 (4.7 Å — partner of D771H Atlas card). N714S is the most conservative substitution in the N714 series — replacing asparagine with serine preserves H-bonding capacity but changes the geometry from amide to hydroxyl. The D713-N714-D771 polar network reorganizes; the new S714 hydroxyl is shorter than asparagine's amide arm. The |ΔΔG| of 0.49 reflects fold accommodation. AlphaMissense's 0.640 is the lowest in the N714 series — borderline above the 0.564 threshold — yet ClinVar Likely Pathogenic with DFNA6 establishes clinical pathogenicity. The mechanism is fine-grained H-bond network adjustment.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.640	**-0.49** kcal/mol	**87.12**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992009621	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/11/08 00:00
Inheritance	DFNA6 hearing loss documented.
WFS1 variant landscape	N714S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- 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 3/4 — Most Druggable. |ΔΔG| = 0.49 — fold survives. AlphaMissense 0.640 borderline + DFNA6 confirm pathogenic consequence.

Mechanism is fine-grained H-bond network reorganization at the D713-N714-D771 polar cluster. Therapeutic strategy: same microregion as N714T, N714K, D771H.

N714S is the THIRD pathogenic substitution at position 714 (with N714T, N714K). Position 714 + the D713-D771-K768 polar network is one of the most multi-variant target hubs in the Atlas.