MOLECULAR ATLAS · VARIANT CARD

WFS1 N714K — Wolframin

Asparagine → Lysine at position 714 in wolframin's C-terminal lumenal domain. ClinVar Conflicting classifications. AlphaMissense 0.992 (near-maximum), DynaMut2 ΔΔG -0.44 kcal/mol (destabilising). The FOURTH Atlas variant at position 714 (with N714T, N714S, and D771H in the same network).

IDENTITY

Variant	N714K (p.Asparagine714Lysine)
DNA change	c.2142C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002831353
Amino acid change	Asparagine (N) → Lysine (K) — polar amide replaced by large positively-charged amine. H-bonding capacity preserved but charge introduced.

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 N714S.
IDR flag	No — pLDDT well above 50 threshold

Position 714 same neighbor environment as N714T/N714S: SER715 (2.4 Å), ASP713 (2.5 Å), PHE770 (4.4 Å), ALA716 (4.4 Å), ASP771 (4.7 Å). Replacing N714 with lysine introduces a positive charge into the D713-D771 polar network — adjacent to two existing negative charges. The K714 amine likely forms salt bridges with D713 and/or D771, restructuring the polar network entirely (where the wild-type N714 amide H-bonded but did not carry charge). The |ΔΔG| of 0.44 reflects fold accommodation. AlphaMissense's 0.992 (near-maximum) confirms severe functional consequence — the charge introduction disrupts the wild-type partner-recognition geometry.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.992	**-0.44** kcal/mol	**87.12**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992013486	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/02/16 00:00
Inheritance	Conflicting classifications.
WFS1 variant landscape	N714K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued — conflicting classifications)

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| = 0.44 — fold survives. AlphaMissense 0.992 (near-maximum) confirms severe functional consequence.

Mechanism is charge introduction into the D713-D771 polar network. Therapeutic strategy: same microregion as N714T, N714S, D771H.

N714K is the FOURTH Atlas variant at position 714 (N714T, N714S, N714K) plus D771H. The D713-N714-D771 polar network is the densest multi-variant target in the lumenal domain — at least four convergent rescue opportunities.