MOLECULAR ATLAS · VARIANT CARD

WFS1 K705N — Wolframin

Lysine → Asparagine at position 705 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic. AlphaMissense 0.990 (near-maximum), DynaMut2 ΔΔG -0.66 kcal/mol (destabilising). A charge-loss variant in the high-confidence lumenal fold.

IDENTITY

Variant	K705N (p.Lysine705Asparagine)
DNA change	c.2115G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003637013
Amino acid change	Lysine (K) → Asparagine (N) — a positively-charged primary-amine-bearing residue replaced by a smaller polar amide. Loss of positive charge and reduced side-chain length, but H-bonding capacity preserved.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 705	**90.00** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 705 sits in the ER lumen in a well-folded region (pLDDT 90).
IDR flag	No — pLDDT well above 50 threshold

Position 705 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places K705 within 5 Å of TYR706 (2.4 Å), PHE704 (2.5 Å), THR778 (3.6 Å, a longer-range contact across the lumenal fold), GLN819 (4.4 Å, another distal contact), and ARG703 (4.5 Å). The neighbors are aromatic-rich (Y706, F704), polar (T778, Q819), and basic (R703, K705 itself). The wild-type lysine at 705 carries a positive charge that likely participates in a salt-bridge or hydrogen-bonding network with the nearby threonine (T778) and glutamine (Q819) residues — both H-bond acceptors. The lysine side chain is long enough (4-carbon alkyl + amine) to reach across to these distal positions, contributing to a folded geometry that brings sequence-distant residues into proximity. Replacing lysine with asparagine removes the positive charge and shortens the side chain. The polar amide of asparagine

can still hydrogen-bond, but it can no longer reach the same distal positions as the lysine's longer chain. The local fold geometry that depends on the K705-T778 or K705-Q819 contact is perturbed. DynaMut2's |ΔΔG| of 0.66 reflects the modest energetic cost of the fold rearrangement. AlphaMissense's 0.990 score captures the severity of the lost functional contact.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.990	**-0.66** kcal/mol	**90.00**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990252901	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/08/16 00:00
Inheritance	Inheritance not specified. ClinVar Pathogenic classification establishes clinical relevance.
WFS1 variant landscape	K705N is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for K705N — ClinVar Pathogenic by review evidence)

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| = 0.66 kcal/mol — fold survives. AlphaMissense 0.990 confirms severe functional consequence.

The mechanism is loss of a long-range electrostatic/H-bond contact (K705 to T778 or Q819) that the wild-type residue's extended side chain made. Therapeutic strategy: site-directed small molecules that bridge the K705-T778-Q819 microregion, restoring the long-range contact the wild-type lysine provided.

This is a good example of how the Atlas's PDB neighbor analysis surfaces distal contacts that sequence-based analysis would miss. T778 is 73 residues away from K705 in sequence but only 3.6 Å away in structure.

K705N's mechanism — loss of long-range structural contact via a long-side-chain residue — is one the Atlas captures well through its 5 Å neighbor extraction. The wild-type lysine reaches across the folded domain to contact residues 73 sequence positions away. Drug discovery here targets the cross-domain contact rather than the local position alone.
