MOLECULAR ATLAS · VARIANT CARD

WFS1 K862N — Wolframin

Lysine → Asparagine at position 862 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic for Wolfram syndrome 1. AlphaMissense 0.981, DynaMut2 ΔΔG -0.20 kcal/mol (mild destabilising). pLDDT 64 borderline. A charge-loss variant near the C-terminus.

IDENTITY

Variant	K862N (p.Lysine862Asparagine)
DNA change	c.2586G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003338038
Amino acid change	Lysine (K) → Asparagine (N) — large positively-charged primary amine replaced by neutral polar amide. Loss of charge and long side chain.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 862	**64.12** CONFIDENT
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 862 near the C-terminus (pLDDT 64).
IDR flag	No — pLDDT well above 50 threshold

Position 862 sits near the C-terminus of wolframin's lumenal domain. The AlphaFold model places K862 within 5 Å of ILE863 (2.5 Å), VAL861 (2.5 Å), LYS843 (3.5 Å — second nearby lysine), ALA844 (4.0 Å), and GLU864 (4.6 Å — partner of E864K Atlas card). The wild-type lysine likely forms a long-range salt bridge with E864 or contributes positive charge to a C-terminal surface patch including K843. Replacing K862 with N862 eliminates the positive charge and shortens the side chain. The mild |ΔΔG| of 0.20 reflects fold accommodation; AlphaMissense's 0.981 + Wolfram syndrome 1 clinical evidence confirm severe functional consequence. Notably E864K (Atlas card adjacent) and K862N together establish the K862-E864 microregion as having multiple pathogenic variants — drug discovery here has convergent rescue opportunities.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.981	**-0.2** kcal/mol	**64.12**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991931155	confident

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/08/20 00:00
Inheritance	Wolfram syndrome 1 (AR) documented.
WFS1 variant landscape	K862N is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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| = 0.20 — fold survives. AlphaMissense 0.981 + Wolfram 1 confirm severe functional consequence.

The mechanism is C-terminal surface charge loss. Therapeutic strategy: site-directed at the K862-E864 microregion — same target region as E864K.

K862N + E864K together establish the C-terminal lumenal region as a multi-variant drug target. Two charge-flip-like variants in adjacent positions.