MOLECULAR ATLAS · VARIANT CARD

WFS1 E249K — Wolframin

Glutamic acid → Lysine at position 249. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance, AlphaMissense 0.596, DynaMut2 ΔΔG -0.64 kcal/mol (destabilising).

IDENTITY

Variant	E249K (p.Glutamic acid249Lysine)
DNA change	c.745G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002866513
Amino acid change	Glutamic acid (E) → Lysine (K)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 249	**86.06** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic (intrinsically disordered)
Position context	N-terminal cytoplasmic (intrinsically disordered)
IDR flag	No — pLDDT well above 50 threshold

> Position 249 sits in N-terminal cytoplasmic (intrinsically disordered). The wild-type residue is negatively charged (glutamate — carboxylate); the mutant is positively charged (lysine — primary amine). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.596

am_class: **likely pathogenic** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.64 kcal/mol

Destabilising · Job 178092133384

PLDDT (ALPHAFOLD)

86.06

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2025/03/17 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	E249K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no conditions catalogued)

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|=0.64 < 2 kcal/mol (fold intact) + AlphaMissense 0.596 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.64 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.596. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
