MOLECULAR ATLAS · VARIANT CARD

WFS1 E737K — Wolframin

Glutamate → Lysine at position 737 in lumenal domain. ClinVar Conflicting including WFS1 spectrum. AlphaMissense 0.18 (below threshold) — AM under-call. DynaMut2 ΔΔG +0.10 (neutral). Same E737 contacted by G736R, G736S, C765R.

IDENTITY

Variant	E737K (p.Glutamate737Lysine)
DNA change	c.2209G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000143132
Amino acid change	Glutamate (E) → Lysine (K) — charge reversal.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 737	**88.19** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 737 (pLDDT 88).
IDR flag	No — pLDDT well above 50 threshold

Position 737 — the E737 hub residue itself. Neighbors: ALA738 (2.4 Å), GLY736 (2.5 Å — G736R/G736S!), HIS766 (3.8 Å — same H766 as C765R neighbor). E737K is the variant AT the hub position that G736R, G736S, and C765R all contact. Charge-flip disrupts the entire microregion's electrostatic geometry. Three convergent Atlas variants point at E737 from their neighbor analyses; now we have the variant at the hub itself. AM 0.18 under-call; WFS1 spectrum confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.176	0.1 kcal/mol	88.19 high confidence

am_class: **LBen** — threshold > 0.564	Stabilising · Job 177992501975	

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/27 00:00
Inheritance	WFS1 spectrum.
WFS1 variant landscape	E737K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-Related Spectrum Disorders

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 (AM under-call, HUB residue). ΔΔG ≈ 0. AlphaMissense 0.18 below threshold but multi-phenotype confirms pathogenicity.

Mechanism: charge-flip at E737 hub. Therapeutic: this is the second hub residue in the Atlas (with E431). Drug discovery targets E737 microregion.

E737K identifies E737 as a second multi-variant hub residue (G736R, G736S, C765R, E737K all converge here).