MOLECULAR ATLAS · VARIANT CARD

WFS1 E301K — Wolframin

Glutamate → Lysine at position 301 in N-terminal cytoplasmic domain. ClinVar Conflicting including Wolfram syndrome 1. AlphaMissense 0.757, ΔΔG -0.63. Charge-flip variant.

IDENTITY

Variant	E301K (p.Glutamate301Lysine)
DNA change	c.901G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000591065
Amino acid change	Glutamate (E) → Lysine (K) — charge reversal.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 301	**73.44** **HIGH CONFIDENCE**
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 301 (pLDDT 73).
IDR flag	No — pLDDT well above 50 threshold

> Position 301 in cytoplasmic domain. Neighbors: TYR302 (2.5 Å), LYS300 (2.5 Å — adjacent existing lysine!), GLU298 (3.6 Å), MET297 (3.8 Å). E301K creates two adjacent positives (K300-K301) where wild-type had K300-E301 alternating. The E298 partner of wild-type E301 loses one of its like-charged neighbors. ΔΔG 0.63 + AM 0.757 + Wolfram 1 confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.757	**-0.63** kcal/mol	**73.44**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992465376	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/09/20 00:00
Inheritance	Wolfram syndrome 1.
WFS1 variant landscape	E301K 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| = 0.63. AlphaMissense 0.757 + Wolfram 1 confirm severe consequence.

Mechanism: charge-flip creating adjacent two-lysine cluster. Therapeutic: site-directed at the 298-302 microregion.

E301K joins the charge-flip class. The 298-302 region has a deliberate alternating positive-negative pattern that the variant disrupts.
