MOLECULAR ATLAS · VARIANT CARD

WFS1 E809K — Wolframin

Glutamate → Lysine at position 809 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic, associated with Wolfram-like syndrome. AlphaMissense 0.718 (moderately pathogenic), DynaMut2 ΔΔG +0.41 kcal/mol — STABILISING. A clean charge-flip variant with structural stabilization.

IDENTITY

Variant	E809K (p.Glutamate809Lysine)
DNA change	c.2425G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215413
Amino acid change	Glutamate (E) → Lysine (K) — negatively-charged carboxylate replaced by positively-charged primary amine. Same charge-flip mechanism as E169K but in a different domain.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 809	**83.44** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 809 in the ER lumen (pLDDT 83).
IDR flag	No — pLDDT well above 50 threshold

Position 809 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places E809 within 5 Å of SER808 (2.5 Å), PHE810 (2.5 Å), SER807 (4.3 Å), LYS811 (4.3 Å), and ILE863 (4.8 Å, long-range). The local environment contains a nearby existing lysine (K811) — the wild-type E809 may have formed an intramolecular salt bridge with K811. Replacing glutamate with lysine reverses the charge sign at position 809. The E809-K811 salt bridge breaks; the local environment now has two adjacent positive charges (K809 and K811) instead of one positive and one negative. The DynaMut2 ΔΔG of +0.41 (stabilising) reflects that the new local geometry is more energetically favorable than the wild-type — likely because both lysines can extend their flexible side chains toward solvent. Yet AlphaMissense places this at 0.718 (moderately pathogenic, above the 0.564 likely-pathogenic threshold) and ClinVar classifies it as Pathogenic. The

mechanism is functional: the lost E809 negative charge was part of the lumenal interaction surface; the introduced K809 creates a new positive patch that disrupts whatever partner recognition the wild-type surface enabled.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.718	**0.41** kcal/mol	**83.44**
am_class: **LPath** — threshold > 0.564	Stabilising · Job 177990267533	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/10/09 00:00
Inheritance	Documented in association with Wolfram-like syndrome. AD-leaning presentation.
WFS1 variant landscape	E809K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram-like syndrome

RESEARCH PATH DECISION TREE

```
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
```

Category 4 — Stable Fold, Function Disrupted. ΔΔG = +0.41 kcal/mol — fold is more stable than wild-type. AlphaMissense 0.718 plus clinical evidence confirm pathogenic mechanism is functional rather than structural.

The mechanism is charge-flip at a lumenal interaction surface — broken E809-K811 salt bridge plus a new positive patch where the wild-type contributed negative charge. Therapeutic strategy: site-directed at the

recognition surface, restoring or compensating for the lost negatively-charged contribution.

E809K joins T361I, L402P, R685P, and others as Atlas variants where ΔΔG is positive (stabilising) but pathogenicity is real. The class is consistent: charge-flip or chemistry-flip variants where the new residue accommodates structurally but disrupts functional recognition. Drug discovery for this class requires AlphaMissense + clinical evidence — ΔΔG alone would miss them.
