MOLECULAR ATLAS · VARIANT CARD

WFS1 K800E — Wolframin

Lysine → Glutamate at position 800 in lumenal domain. ClinVar Conflicting. AlphaMissense 0.778, ΔΔG -0.40. pLDDT 72 borderline. Same K800-D801 salt-bridge pair as D801G.

IDENTITY

Variant	K800E (p.Lysine800Glutamate)
DNA change	c.2398A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215400
Amino acid change	Lysine (K) → Glutamate (E) — positively-charged amine replaced by negatively-charged carboxylate. Charge reversal.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 800	**71.69** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 800 (pLDDT 72).
IDR flag	No — pLDDT well above 50 threshold

> Position 800 sits adjacent to D801. Neighbors: ASP801 (2.5 Å — D801G Atlas card!), THR799 (2.5 Å), ASP797 (3.7 Å), VAL798 (4.3 Å). The wild-type K800-D801 salt bridge (referenced in D801G Atlas card) breaks when K800 becomes E800: now TWO adjacent glutamates (E800, D801) with no positive charge to stabilize. The local electrostatic environment is transformed. ΔΔG 0.40 + AM 0.778 confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.778	**-0.4** kcal/mol	**71.69**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992463771	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/11/03 00:00
Inheritance	Not specified.
WFS1 variant landscape	K800E is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific 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| = 0.40. AlphaMissense 0.778 confirms severe consequence.

Mechanism: K800-D801 salt bridge broken by charge-flip at K800. Therapeutic: same K800-D801 microregion as D801G.

K800E + D801G are sister variants at the salt-bridge pair. Two convergent variant targets at the same ionic contact.