

WFS1 E824K — Wolframin

Glutamate → Lysine at position 824 in luminal domain. ClinVar Conflicting including DFNA6. AlphaMissense 0.566 (borderline), $\Delta\Delta G$ -0.13.

IDENTITY

Variant	E824K (p.Glutamate824Lysine)
DNA change	c.2470G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000166612
Amino acid change	Glutamate (E) → Lysine (K) — charge reversal.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 824	89.81 HIGH CONFIDENCE
Domain	C-terminal luminal domain (653-869)
Position context	C-terminal luminal domain · position 824 (pLDDT 90).
IDR flag	No — pLDDT well above 50 threshold

Position 824 in luminal domain. Neighbors: PHE825 (2.4 Å — W700-F825 π -stacking partner!), ILE823 (2.5 Å), TRP700 (3.5 Å — direct contact with W700 Cat 2 region!), SER846 (3.7 Å). E824 sits in direct contact with W700 and F825 — the same aromatic cluster identified in W700C and T699P Atlas cards. The wild-type E824 negative charge contributes to this microregion. Charge-flipping to K824 disrupts the local environment supporting W700-F825 π -stacking. Mild $\Delta\Delta G$; AM 0.566 borderline + DFNA6 confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE 0.566 am_class: LPath — threshold > 0.564	DYNAMUT2 $\Delta\Delta G$ -0.13 kcal/ mol	PLDDT (ALPHAFOLD) 89.81 high confidence
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Destabilising · Job
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CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2024/03/21 00:00

Inheritance

DFNA6.

WFS1 variant landscape

E824K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

RESEARCH PATH DECISION TREE

$\Delta\Delta G < 2$ + binding site affected → CATEGORY 3 – docking experiments $\Delta\Delta G$ 2–4 → CATEGORY 2 – pharmacological chaperones $\Delta\Delta G > 4$ → CATEGORY 1 – gene therapy pLDDT < 50 → CATEGORY 5 – IDR, experimental only Stable fold + functional site hit → CATEGORY 4 – site-specific docking

Category 3/4 — Most Druggable. $|\Delta\Delta G| = 0.13$. AlphaMissense 0.566 borderline + DFNA6 confirm severe consequence.

Mechanism: charge-flip in the W700-F825 aromatic cluster. Therapeutic: same W700-F825 microregion (with W700S/C, T699P/M).

E824K is the FIFTH variant converging on the W700-F825 π -stacking microregion. Drug discovery here has unusually dense convergence.