MOLECULAR ATLAS · VARIANT CARD

WFS1 E864K — Wolframin

Glutamate → Lysine at position 864 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic/Likely pathogenic for DFNA6 hearing loss. AlphaMissense 0.842, DynaMut2 ΔΔG -0.26 kcal/mol (destabilising). pLDDT 59 borderline. A charge-flip variant in a low-confidence region.

IDENTITY

Variant	E864K (p.Glutamate864Lysine)
DNA change	c.2590G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000004526
Amino acid change	Glutamate (E) → Lysine (K) — negatively-charged carboxylate-bearing residue replaced by positively-charged primary amine-bearing residue. Same charge-flip mechanism as E169K, E809K.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 864	**59.28** CONFIDENT
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 864 near the C-terminus (pLDDT 59 — borderline confidence).
IDR flag	No — pLDDT well above 50 threshold

Position 864 sits in wolframin's C-terminal lumenal domain near the C-terminus. The AlphaFold model places E864 within 5 Å of HIS865 (2.4 Å), ILE863 (2.4 Å), ASP866 (4.7 Å), and LYS862 (4.8 Å). The local environment carries multiple charged residues (H865, D866, K862), suggesting a charged surface patch near the C-terminus. Replacing glutamate with lysine reverses the charge sign at 864. The wild-type negative charge contributed to the surface patch character; the new positive charge changes the surface electrostatics entirely. The nearby D866 (4.7 Å) was likely electrostatically complementary to E864's negative charge through the H865 bridge; the variant K864 now has a charge same-sign as nearby H865 (often protonated in mildly acidic ER lumen) and opposite to D866 — local rearrangement is required. The |ΔΔG| of 0.26 is modest. AlphaMissense's 0.842 plus DFNA6

clinical evidence confirm pathogenic mechanism. The pLDDT of 59 is borderline; the structural details deserve wet-lab confirmation, but the charge-flip mechanism is clear.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.842	**-0.26** kcal/mol	**59.28**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991406993	confident

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2024/11/08 00:00
Inheritance	Autosomal dominant DFNA6 documented.
WFS1 variant landscape	E864K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Rare genetic deafness
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

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 (pLDDT caveat). |ΔΔG| = 0.26 kcal/mol — fold survives. AlphaMissense 0.842 + DFNA6 confirm pathogenic functional consequence. pLDDT 59 borderline — wet-lab validation recommended.

The mechanism is charge-flip at a C-terminal lumenal surface patch

involving H865, D866, K862. Therapeutic strategy: site-directed at the C-terminal surface — restoring or compensating for the lost negative charge.

E864K joins the Atlas's charge-flip variant class (E169K, E809K). Each disrupts a recognition surface through opposite-sign charge introduction. The class is consistent across the cytoplasmic and lumenal domains.
