MOLECULAR ATLAS · VARIANT CARD

WFS1 K634T — Wolframin

Lysine → Threonine at position 634 inside wolframin's tenth transmembrane helix (TM10). ClinVar Pathogenic, associated with DFNA6 hearing loss. AlphaMissense 0.883, DynaMut2 ΔΔG -0.32 kcal/mol (destabilising). A charge-loss variant in a TM helix.

IDENTITY

Variant	K634T (p.Lysine634Threonine)
DNA change	c.1901A>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000004524
Amino acid change	Lysine (K) → Threonine (T) — large positively-charged primary amine replaced by small polar hydroxyl. Both can hydrogen-bond, but charge is lost and side-chain length is dramatically reduced.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 634	**82.69** HIGH CONFIDENCE
Domain	TM10 (632-652), helical transmembrane
Position context	TM10 (residues 632–652) · position 634 is at the very start of TM10, in the membrane interface region (pLDDT 83).
IDR flag	No — pLDDT well above 50 threshold

Position 634 sits at the start of TM10. The AlphaFold model places K634 within 5 Å of LEU635 (2.5 Å), VAL633 (2.5 Å), SER631 (3.8 Å), SER630 (4.0 Å), and MET632 (4.3 Å). The local environment is hydrophobic-rich with two nearby serines (S630, S631) — characteristic of a TM-helix start in the lipid headgroup region. The wild-type lysine at 634 is positioned where its long alkyl chain can extend toward the membrane-water interface and its primary amine can engage phospholipid headgroups. This is a 'positive-inside rule' position — basic residues at the cytoplasmic end of TM helices are stabilizing for membrane orientation. Replacing lysine with threonine removes this positive-inside anchor. The new T634 is small and polar but cannot reach the membrane interface or engage headgroups. TM10's orientation may shift slightly to compensate. The |ΔΔG| of 0.32 reflects modest structural cost.

AlphaMissense's 0.883 score plus the DFNA6 clinical association confirm pathogenic consequence — likely from altered TM10 topology and downstream effects on helix-helix packing (notably the TM3-TM10 interface that T641K disrupts).

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.883

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.32 kcal/mol

Destabilising · Job 177990265685

PLDDT (ALPHAFOLD)

82.69

high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	no assertion criteria provided
Last evaluated	2002/01/01 00:00
Inheritance	Autosomal dominant DFNA6 hearing loss documented.
WFS1 variant landscape	K634T 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

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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| = 0.32 kcal/mol — fold survives. AlphaMissense 0.883 + DFNA6 clinical association confirm pathogenic functional consequence.

The mechanism is loss of the positive-inside anchor at the TM10 cytoplasmic end, with secondary effect on TM10's overall topology and TM3-TM10

packing. Therapeutic strategy: site-directed at the TM10 N-terminal membrane interface.

Combined with T641K (Atlas card adjacent — TM10 mid-helix with TM3-TM10 interface mechanism), drug discovery targeting TM10 has two convergent variant targets.

K634T illustrates the 'positive-inside rule' in WFS1 — basic residues at TM helix termini are deliberate anchors. Their loss perturbs membrane topology even when overall fold survives. The Atlas captures this through the neighbor analysis at the cytoplasmic end of TM10.
