MOLECULAR ATLAS · VARIANT CARD

WFS1 A326E — Wolframin

Alanine → Glutamate at position 326 inside TM1. ClinVar Likely pathogenic, DFNA6 hearing loss. AlphaMissense 0.940, DynaMut2 ΔΔG -0.33 kcal/mol (destabilising). Charge-introduction variant in TM1.

IDENTITY

Variant	A326E (p.Alanine326Glutamate)
DNA change	c.977C>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV004687962
Amino acid change	Alanine (A) → Glutamate (E) — small methyl-bearing hydrophobic replaced by negatively-charged carboxylate-bearing residue.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 326	**76.88** HIGH CONFIDENCE
Domain	TM1 (314-334), helical transmembrane
Position context	TM1 (residues 314–334) · position 326 mid-helix, bilayer-embedded (pLDDT 77).
IDR flag	No — pLDDT well above 50 threshold

Position 326 sits in TM1. The AlphaFold model places A326 within 5 Å of ASN325 (2.5 Å), LEU327 (2.5 Å), HIS322 (3.6 Å), HIS323 (3.7 Å — partner of H323R Atlas card), and PHE329 (4.2 Å). The local environment includes two adjacent histidines (H322, H323). Replacing alanine with glutamate introduces a negative charge into the bilayer-embedded TM1 environment. The carboxylate can interact with the nearby H322/H323 imidazoles when they're protonated, potentially forming a stable salt-bridge that differs from the wild-type fold geometry. But this rearrangement comes at a structural cost. The |ΔΔG| of 0.33 reflects fold accommodation. AlphaMissense's 0.940 + DFNA6 confirm severe functional consequence. Mechanism is charge introduction at the TM1 H322-H323 cluster.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.940	**-0.33** kcal/mol	**76.88**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992007843	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2025/08/25 00:00
Inheritance	DFNA6 hearing loss documented.
WFS1 variant landscape	A326E 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| = 0.33 — fold survives. AlphaMissense 0.940 + DFNA6 confirm severe functional consequence.

Mechanism is charge introduction into the TM1 H322-H323 cluster. Therapeutic strategy: site-directed at TM1 mid-helix.

A326E joins the TM1 variant cluster (W314R, H313Y, H323R, T321R, T321P, A326E). Six variants in or near TM1 in the Atlas — the helix is a recurring therapeutic target region.