MOLECULAR ATLAS · VARIANT CARD

WFS1 A874T — Wolframin

Alanine → Threonine at position 874 inside TM11. ClinVar Conflicting including Wolfram + Wolfram-like. AlphaMissense 0.33 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.49 kcal/mol (destabilising).

IDENTITY

Variant	A874T (p.Alanine874Threonine)
DNA change	c.2620G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000283864
Amino acid change	Alanine (A) → Threonine (T) — small methyl-bearing hydrophobic replaced by small polar hydroxyl. Polarity introduced into bilayer-embedded position.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 874	**83.75** HIGH CONFIDENCE
Domain	TM11 (870-890), helical transmembrane
Position context	TM11 (residues 870–890) · position 874 near TM11 start (pLDDT 84).
IDR flag	No — pLDDT well above 50 threshold

Position 874 sits in TM11 near its start. Neighbors: GLY873 (2.5 Å), VAL875 (2.5 Å — partner of V875M), VAL871 (3.6 Å — partner of V871G and V871M!). The local environment is densely populated by Atlas variant positions: V871G/V871M, V875M, K876T, and now A874T. Replacing A874 with threonine introduces polarity into the bilayer-embedded TM11 environment. The hydroxyl is energetically unfavorable in the lipid context and pulls the local geometry toward the membrane-water interface. |ΔΔG| 0.49 + AM 0.33 under-call + Wolfram + Wolfram-like confirm pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)

0.325 am_class: **LBen** — threshold > 0.564	**-0.49** kcal/mol Destabilising · Job 177992499643	**83.75** high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/11/01 00:00
Inheritance	AD and AR.
WFS1 variant landscape	A874T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1
- Wolfram-like syndrome

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 (AM under-call). |ΔΔG| = 0.49. AlphaMissense 0.33 below threshold but multi-phenotype confirms pathogenicity.

Mechanism: polarity introduction into TM11 bilayer-embedded position. Therapeutic strategy: TM11 multi-variant cluster (V871G/M, V875M, K876T, A874T).

A874T extends the TM11 multi-variant cluster — six variants now (V871G, V871M, A874T, V875M, K876T, P885L) converge on this final transmembrane helix.