MOLECULAR ATLAS · VARIANT CARD

WFS1 K876T — Wolframin

Lysine → Threonine at position 876 inside TM11. ClinVar Conflicting including T2D. AlphaMissense 0.29 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.49.

IDENTITY

Variant	K876T (p.Lysine876Threonine)
DNA change	c.2627A>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000281647
Amino acid change	Lysine (K) → Threonine (T) — long positively-charged amine replaced by small polar hydroxyl. Loss of charge.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 876	**83.94** HIGH CONFIDENCE
Domain	TM11 (870-890), helical transmembrane
Position context	TM11 (residues 870–890) · position 876 (pLDDT 84).
IDR flag	No — pLDDT well above 50 threshold

> Position 876 in TM11. Neighbors: PHE877 (2.4 Å), VAL875 (2.5 Å — partner of V875M), HIS872 (3.7 Å — same H872 in V871G cluster). K876T joins the TM11 multi-variant cluster. The wild-type K876 likely serves as a 'positive-inside rule' anchor at the TM11 cytoplasmic end; losing it perturbs TM11 topology. AM 0.29 under-call; T2D confirms pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.287

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.49 kcal/mol

PLDDT (ALPHAFOLD)

83.94

high confidence

Destabilising · Job 177992495245

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/08/22 00:00
Inheritance	T2D documented.
WFS1 variant landscape	K876T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Type 2 diabetes mellitus

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 0.29 below threshold but T2D confirms pathogenicity.

Mechanism: loss of positive-inside anchor at TM11. Therapeutic: TM11 multi-variant cluster (V871G/M, V875M, A874T, P885L).

K876T is the 7th TM11 cluster variant — the helix is one of the most variant-dense in the Atlas.