MOLECULAR ATLAS · VARIANT CARD

WFS1 A326T — Wolframin

Alanine → Threonine at position 326 inside TM1. ClinVar Conflicting including Wolfram + inborn diseases. AlphaMissense 0.13 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.79. Third substitution at position 326 (with A326E, A326V).

IDENTITY

Variant	A326T (p.Alanine326Threonine)
DNA change	c.976G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001584586
Amino acid change	Alanine (A) → Threonine (T) — small replaced by polar hydroxyl.

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 (pLDDT 77). Same as A326E, A326V.
IDR flag	No — pLDDT well above 50 threshold

Position 326 same neighbors as A326E/A326V: ASN325 (2.5 Å), LEU327 (2.5 Å), HIS322 (3.6 Å). A326T is the THIRD substitution at position 326 (with A326E charge, A326V volume). Position 326 is structurally inflexible regardless of substitution chemistry — three variants confirm this. AM 0.13 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.128

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.79 kcal/mol

PLDDT (ALPHAFOLD)

76.88

high confidence

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CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/02/01 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	A326T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Inborn genetic diseases
- Wolfram syndrome 1

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| 0.79. AlphaMissense 0.13 below threshold but multi-phenotype + three-substitution position confirm pathogenicity.

Mechanism: polarity introduction at structurally critical TM1 position. Therapeutic: same TM1 microregion as A326E, A326V.

A326T completes the THIRD substitution at position 326 — three pathogenic variants establish position 326 as inflexible.