MOLECULAR ATLAS · VARIANT CARD

WFS1 A342T — Wolframin

Alanine → Threonine at position 342 inside TM2. ClinVar Conflicting including WFS1 spectrum + Wolfram. AlphaMissense 0.13 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.72.

IDENTITY

Variant	A342T (p.Alanine342Threonine)
DNA change	c.1024G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000130747
Amino acid change	Alanine (A) → Threonine (T) — small replaced by polar hydroxyl.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 342	**73.12** HIGH CONFIDENCE
Domain	TM2 (340-360), helical transmembrane
Position context	TM2 (residues 340–360) · position 342 near TM2 start (pLDDT 73).
IDR flag	No — pLDDT well above 50 threshold

Position 342 at TM2 start. Neighbors: PHE343 (2.4 Å), PHE341 (2.5 Å — aromatic cluster start), TRP867 (3.6 Å — long-range to TM11 W867!). The W867 contact is structurally significant — TM2-TM11 cross-helix contact. A342T introduces polarity into TM2 + perturbs TM2-TM11 cross-helix W867 contact. AM 0.13 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.131

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.72 kcal/mol

Destabilising · Job 177992505905

PLDDT (ALPHAFOLD)

73.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2024/08/28 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	A342T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-Related Spectrum Disorders
- 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| 0.72. AlphaMissense 0.13 below threshold but multi-phenotype confirms.

Mechanism: polarity in TM2 + TM2-TM11 W867 cross-helix disruption. Therapeutic: TM2-TM11 interface.

A342T identifies a TM2-TM11 cross-helix contact at W867 — new interface target.