MOLECULAR ATLAS · VARIANT CARD

WFS1 M357T — Wolframin

Methionine → Threonine at position 357. Transmembrane helix 2. ClinVar Uncertain significance, AlphaMissense 0.953, DynaMut2 ΔΔG +0.18 kcal/mol (stabilising).

IDENTITY

Variant	M357T (p.Methionine357Threonine)
DNA change	c.1070T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003671232
Amino acid change	Methionine (M) → Threonine (T)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 357	**93.44** HIGH CONFIDENCE
Domain	Transmembrane helix 2
Position context	Inside Transmembrane helix 2 · position 357 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

> Position 357 sits in a transmembrane helix (Transmembrane helix 2). Wolframin has eleven such helices anchoring it in the ER membrane; substitutions inside the bilayer-embedded segments can disrupt helix packing, lipid contacts, and the overall ER topology of the protein. The wild-type residue is hydrophobic sulfur (methionine); the mutant is small polar (threonine — hydroxyl). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.953

am_class: **likely pathogenic** — threshold > 0.564

DYNAMUT2 ΔΔG

0.18 kcal/mol

Stabilising · Job 178092099903

PLDDT (ALPHAFOLD)

93.44

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2024/06/23 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	M357T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no conditions catalogued)

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|=0.18 < 2 kcal/mol (fold intact) + AlphaMissense 0.953 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.18 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.953. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
