MOLECULAR ATLAS · VARIANT CARD

WFS1 T337I — Wolframin

Threonine → Isoleucine at position 337 in a connecting loop. ClinVar Likely pathogenic for Wolfram syndrome 1. AlphaMissense 0.865, DynaMut2 ΔΔG -0.48 kcal/mol (destabilising). pLDDT 65 borderline.

IDENTITY

Variant	T337I (p.Threonine337Isoleucine)
DNA change	c.1010C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002203515
Amino acid change	Threonine (T) → Isoleucine (I) — small polar hydroxyl replaced by branched aliphatic hydrophobic. Loss of H-bonding.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 337	**65.12** CONFIDENT
Domain	Connecting loop
Position context	Connecting loop · position 337 in a borderline-confidence region (pLDDT 65).
IDR flag	No — pLDDT well above 50 threshold

> Position 337 sits in a connecting loop near TM2. The AlphaFold model places T337 within 5 Å of ILE338 (2.4 Å), LEU336 (2.5 Å), ASN335 (4.1 Å), ASP339 (4.2 Å), and PHE340 (4.4 Å). The local environment is mixed polar-hydrophobic. The wild-type threonine's hydroxyl likely H-bonds with the nearby N335 or D339. Replacing it with isoleucine eliminates the H-bonding capacity. The fold absorbs the substitution (|ΔΔG| 0.48), but the local H-bond network reorganizes. AlphaMissense 0.865 + Wolfram 1 confirm pathogenic consequence. The mechanism is loss of T337's H-bonding role in the loop's polar network. pLDDT 65 is borderline; structural details deserve wet-lab confirmation.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.865

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.48 kcal/mol

Destabilising · Job 177992006426

PLDDT (ALPHAFOLD)

65.12

confident

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/08/26 00:00
Inheritance	Wolfram syndrome 1 (AR) documented.
WFS1 variant landscape	T337I is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- 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 (pLDDT caveat). |ΔΔG| = 0.48 — fold survives. AlphaMissense 0.865 + Wolfram 1 confirm pathogenic consequence. pLDDT 65 borderline.

Mechanism is loss of T337 H-bonding role. Therapeutic strategy: site-directed at the connecting loop polar network.

T337I is another threonine-to-isoleucine variant in the Atlas (with T361I). The class of T→I substitutions, removing H-bonding capacity, recurs at multiple positions and is consistently pathogenic.