MOLECULAR ATLAS · VARIANT CARD

WFS1 T461I — Wolframin

Threonine → Isoleucine at position 461 in a connecting loop. ClinVar Conflicting including Wolfram syndrome 1. AlphaMissense 0.30 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.30 kcal/mol. Adjacent to E462G (Atlas card).

IDENTITY

Variant	T461I (p.Threonine461Isoleucine)
DNA change	c.1382C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000229636
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 461	**86.12** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 461 (pLDDT 86).
IDR flag	No — pLDDT well above 50 threshold

Position 461 sits in a connecting loop, immediately upstream of E462 (E462G Atlas card). Neighbors: GLU462 (2.5 Å — the E462G variant position!), ALA460 (2.5 Å), ALA458 (3.6 Å). The E462 contact at 2.5 Å places T461 in direct sequence contact with the E462G pathogenic variant. The wild-type T461 hydroxyl likely H-bonds with E462's carboxylate, stabilizing the local loop geometry. Replacing T461 with isoleucine eliminates the H-bonding capacity; the E462 carboxylate loses its sequence-neighbor H-bond partner. |ΔΔG| 0.30 + AM 0.30 below threshold + Wolfram syndrome 1 confirm pathogenicity. The mechanism is loss of T461-E462 H-bond — perturbing the same loop microregion that E462G disrupts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)

0.296 am_class: **LBen** — threshold > 0.564	**-0.3** kcal/mol Destabilising · Job 177992494367	**86.12** high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2015/12/31 00:00
Inheritance	Wolfram syndrome 1.
WFS1 variant landscape	T461I 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 (AM under-call). |ΔΔG| = 0.30. AlphaMissense 0.30 below threshold but Wolfram 1 confirms pathogenicity.

Mechanism: loss of T461-E462 H-bond. Therapeutic strategy: same E462 loop microregion as E462G.

T461I + E462G are sister variants at adjacent positions — both disrupt the T461-E462 H-bond geometry.