

WFS1 T440I — Wolframin

Threonine → Isoleucine at position 440. Transmembrane helix 5. ClinVar Uncertain significance, AlphaMissense 0.761, DynaMut2 $\Delta\Delta G$ -0.38 kcal/mol (destabilising).

IDENTITY

Variant	T440I (p.Threonine440Isoleucine)
DNA change	c.1319C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001352971
Amino acid change	Threonine (T) → Isoleucine (I)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 440	91.00 HIGH CONFIDENCE
Domain	Transmembrane helix 5
Position context	Inside Transmembrane helix 5 · position 440 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 440 sits in a transmembrane helix (Transmembrane helix 5). 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 small polar (threonine — hydroxyl); the mutant is medium hydrophobic (isoleucine — branched). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.761am_class: **likely pathogenic** — threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-0.38** kcal/mol

Destabilising · Job 178092119552

PLDDT (ALPHAFOLD)

91.00

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/06/10 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	T440I is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)
	<ul style="list-style-type: none">• Inborn genetic diseases• Autosomal dominant nonsyndromic hearing loss 6• Type 2 diabetes mellitus• Wolfram-like syndrome• Wolfram syndrome 1• Cataract 41

RESEARCH PATH DECISION TREE

$\Delta\Delta G < 2$ + binding site affected → CATEGORY 3 – docking experiments $\Delta\Delta G 2-4$ → CATEGORY 2 – pharmacological chaperones $\Delta\Delta G > 4$ → CATEGORY 1 – gene therapy pLDDT < 50 → CATEGORY 5 – IDR, experimental only Stable fold + functional site hit → CATEGORY 4 – site-specific docking

Category 3/4 — Most Druggable

$|\Delta\Delta G|=0.38 < 2$ kcal/mol (fold intact) + AlphaMissense 0.761 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution ($|\Delta\Delta G|=0.38$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.761. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.