MOLECULAR ATLAS · VARIANT CARD

WFS1 T827I — Wolframin

Threonine → Isoleucine at position 827. C-terminal ER-lumenal (calcium binding. ClinVar Uncertain significance/Uncertain risk allele, AlphaMissense 0.912, DynaMut2 ΔΔG +0.56 kcal/mol (stabilising).

IDENTITY

Variant	T827I (p.Threonine827Isoleucine)
DNA change	c.2480C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000930354
Amino acid change	Threonine (T) → Isoleucine (I)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 827	**88.19** HIGH CONFIDENCE
Domain	C-terminal ER-lumenal (calcium binding, calmodulin, chaperone)
Position context	C-terminal lumenal domain · position 827 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

> Position 827 sits in the C-terminal lumenal domain (residues 653–869), wolframin's largest soluble region. This domain projects into the ER lumen and is implicated in calcium handling, ER stress sensing, and protein–protein interactions with ATF6 and Na+/K+ ATPase β1. 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

0.912

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

DYNAMUT2 ΔΔG

0.56 kcal/mol

Stabilising · Job 178092145594

PLDDT (ALPHAFOLD)

88.19

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE/UNCERTAIN RISK ALLELE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2016/01/01 00:00
Inheritance	Autosomal recessive Wolfram syndrome 1 phenotype documented.
WFS1 variant landscape	T827I is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1
- Type 2 diabetes mellitus

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|=0.56 < 2 kcal/mol (fold intact) + AlphaMissense 0.912 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.56 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.912. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
