MOLECULAR ATLAS · VARIANT CARD

WFS1 I845T — Wolframin

Isoleucine → Threonine at position 845. C-terminal ER-lumenal (calcium binding. ClinVar Uncertain significance, AlphaMissense 0.944, DynaMut2 ΔΔG -2.33 kcal/mol (destabilising).

IDENTITY

Variant	I845T (p.Isoleucine845Threonine)
DNA change	c.2534T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003590746
Amino acid change	Isoleucine (I) → Threonine (T)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 845	**89.25** HIGH CONFIDENCE
Domain	C-terminal ER-lumenal (calcium binding, calmodulin, chaperone)
Position context	C-terminal lumenal domain · position 845 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

> Position 845 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 medium hydrophobic (isoleucine — branched); 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

0.944

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

DYNAMUT2 ΔΔG

-2.33 kcal/mol

Destabilising · Job 178092101091

PLDDT (ALPHAFOLD)

89.25

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2024/05/14 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	I845T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Autosomal dominant nonsyndromic hearing loss 6
- Cataract 41
- Wolfram syndrome 1
- Wolfram-like syndrome
- 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 2 — Moderately Destabilizing

|ΔΔG|=2.33 in the 2–4 range. Pharmacological chaperone candidate.

RareResearch.AI · WFS1 Molecular Atlas · Generated by wolfram-variant-card skill

Every assumption documented.