MOLECULAR ATLAS · VARIANT CARD

WFS1 F417S — Wolframin

Phenylalanine → Serine at position 417. Transmembrane helix 4. ClinVar Uncertain significance, AlphaMissense 0.657, DynaMut2 ΔΔG -2.01 kcal/mol (destabilising).

IDENTITY

Variant	F417S (p.Phenylalanine417Serine)
DNA change	c.1250T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003675121
Amino acid change	Phenylalanine (F) → Serine (S)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 417	**87.75** HIGH CONFIDENCE
Domain	Transmembrane helix 4
Position context	Inside Transmembrane helix 4 · position 417 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

> Position 417 sits in a transmembrane helix (Transmembrane helix 4). 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 large aromatic hydrophobic (phenylalanine); the mutant is small polar (serine — hydroxyl). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.657	**-2.01** kcal/mol	**87.75**
am_class: **likely pathogenic** — threshold > 0.564	Destabilising · Job 178092129019	high confidence

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CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2024/07/19 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	F417S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no conditions catalogued)

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|=2.01 in the 2–4 range. Pharmacological chaperone candidate.

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