MOLECULAR ATLAS · VARIANT CARD

WFS1 F374L — Wolframin

Phenylalanine → Leucine at position 374. Transmembrane helix 3. ClinVar Uncertain significance, AlphaMissense 0.983, DynaMut2 ΔΔG +0.03 kcal/mol (stabilising).

IDENTITY

Variant	F374L (p.Phenylalanine374Leucine)
DNA change	c.1122C>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001966944
Amino acid change	Phenylalanine (F) → Leucine (L)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 374	**83.25** HIGH CONFIDENCE
Domain	Transmembrane helix 3
Position context	Inside Transmembrane helix 3 · position 374 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

> Position 374 sits in a transmembrane helix (Transmembrane helix 3). 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 medium hydrophobic (leucine — branched). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.983

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

DYNAMUT2 ΔΔG

0.03 kcal/mol

Stabilising · Job 178092092901

PLDDT (ALPHAFOLD)

83.25

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/08/10 00:00
Inheritance	Autosomal recessive Wolfram syndrome 1 phenotype documented.
WFS1 variant landscape	F374L 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

|ΔΔG|=0.03 < 2 kcal/mol (fold intact) + AlphaMissense 0.983 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.03 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.983. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
