MOLECULAR ATLAS · VARIANT CARD

WFS1 L514F — Wolframin

Leucine → Phenylalanine at position 514. Transmembrane helix 7. ClinVar Uncertain significance, AlphaMissense 0.597, DynaMut2 ΔΔG -1.32 kcal/mol (destabilising).

IDENTITY

Variant	L514F (p.Leucine514Phenylalanine)
DNA change	c.1540C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001208897
Amino acid change	Leucine (L) → Phenylalanine (F)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 514	**88.12** HIGH CONFIDENCE
Domain	Transmembrane helix 7
Position context	Inside Transmembrane helix 7 · position 514 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

> Position 514 sits in a transmembrane helix (Transmembrane helix 7). 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 medium hydrophobic (leucine — branched); the mutant is large aromatic hydrophobic (phenylalanine). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.597

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

DYNAMUT2 ΔΔG

-1.32 kcal/mol

Destabilising · Job 178092155662

PLDDT (ALPHAFOLD)

88.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2022/01/01 00:00
Inheritance	Autosomal recessive Wolfram syndrome 1 phenotype documented.
WFS1 variant landscape	L514F is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Optic atrophy
- 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|=1.32 < 2 kcal/mol (fold intact) + AlphaMissense 0.597 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=1.32 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.597. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.