MOLECULAR ATLAS · VARIANT CARD

WFS1 V536L — Wolframin

Valine → Leucine at position 536. Transmembrane helix 8. ClinVar Uncertain significance, AlphaMissense 0.659, DynaMut2 ΔΔG -0.40 kcal/mol (destabilising).

IDENTITY

Variant	V536L (p.Valine536Leucine)
DNA change	c.1606G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002151042
Amino acid change	Valine (V) → Leucine (L)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 536	**90.62** HIGH CONFIDENCE
Domain	Transmembrane helix 8
Position context	Inside Transmembrane helix 8 · position 536 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

> Position 536 sits in a transmembrane helix (Transmembrane helix 8). 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 small hydrophobic (valine — branched); 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

0.659

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

DYNAMUT2 ΔΔG

-0.4 kcal/mol

Destabilising · Job 178092128557

PLDDT (ALPHAFOLD)

90.62

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2024/09/06 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	V536L 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 3/4 — Most Druggable

|ΔΔG|=0.40 < 2 kcal/mol (fold intact) + AlphaMissense 0.659 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.40 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.659. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
