MOLECULAR ATLAS · VARIANT CARD

WFS1 F264L — Wolframin

Phenylalanine → Leucine at position 264 in N-terminal cytoplasmic domain. ClinVar Conflicting including Wolfram-like syndrome. AlphaMissense 0.29 (below threshold) — AM under-call. DynaMut2 ΔΔG +0.19 kcal/mol (stabilising). pLDDT 47 — Category 5 IDR territory.

IDENTITY

Variant	F264L (p.Phenylalanine264Leucine)
DNA change	c.792C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000504707
Amino acid change	Phenylalanine (F) → Leucine (L) — aromatic hydrophobic replaced by branched aliphatic hydrophobic. Aromatic π-system lost.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 264	**47.03** BELOW IDR THRESHOLD
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 264 in a borderline-IDR region (pLDDT 47).
IDR flag	YES — pLDDT 47.03 is below 50 threshold (route to Cat 5)

Position 264 sits in wolframin's N-terminal cytoplasmic domain at the boundary of the IDR. pLDDT of 47 is BELOW the 50 threshold — the Atlas formally classifies this position as Category 5 (IDR exclusion). DynaMut2 predictions in this region are not fully trustworthy. Neighbors: LEU263 (2.5 Å), LEU265 (2.5 Å), SER261 (4.1 Å). The neighbor sparsity is itself an IDR signature. AlphaMissense's 0.29 is below threshold. The Conflicting ClinVar classifications and the IDR localization together flag this variant as one where computational drug discovery should pause for wet-lab characterization.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.287	**0.19** kcal/mol	**47.03**
am_class: **LBen** — threshold > 0.564	Stabilising · Job 177992494543	BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/06/12 00:00
Inheritance	WFS1-related disorder + Wolfram-like syndrome documented.
WFS1 variant landscape	F264L is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-related disorder
- Wolfram-like syndrome

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 5 — IDR Exclusion (borderline). pLDDT 47 below the 50 threshold. AlphaMissense 0.29 below threshold. DynaMut2 prediction not trustworthy.

The Atlas routes Category 5 variants to wet-lab characterization rather than computational drug discovery.

F264L is the latest Category 5 IDR-region variant in the Atlas. Wet-lab validation required before therapeutic strategy is set.