MOLECULAR ATLAS · VARIANT CARD

WFS1 M474L — Wolframin

Met→Leu p474 TM5 AM=0.07 ddg=-0.21 pLDDT=65. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	M474L (p.Methionine474Leucine)
DNA change	c.1420A>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003590694
Amino acid change	methionine chemistry lost

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 474	**64.94** CONFIDENT
Domain	TM5 (465-485), helical transmembrane
Position context	TM5 (465-485)
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: SER473 (2.5 Å — partner of S469L region), PRO475 (2.5 Å), LEU471 (4.1 Å). Second TM5 variant. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.068

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.21 kcal/mol

Destabilising · Job 177992524634

PLDDT (ALPHAFOLD)

64.94

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2024/12/20 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	M474L is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific 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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Cat 4 — see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally identified. Therapeutic strategy: site-directed at contacts identified above, or wet-lab validation if pLDDT borderline/below 50.

TM5 cluster (with S469L).
