MOLECULAR ATLAS · VARIANT CARD

WFS1 T490A — Wolframin

Thr→Ala p490 loop AM=0.08 ddg=-0.34 pLDDT=81. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	T490A (p.Threonine490Alanine)
DNA change	c.1468A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000505052
Amino acid change	H-bond loss + side-chain reduction

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 490	**81.38** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: VAL491 (2.5 Å), ILE489 (2.5 Å — I489M!), LEU499 (3.5 Å — L499F partner!). Multi-variant target. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.082

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.34 kcal/mol

Destabilising · Job 177992522848

PLDDT (ALPHAFOLD)

81.38

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2016/06/02 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	T490A 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 3/4 — 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.

T490A + I489M + L499F cluster.

RareResearch.AI · WFS1 Molecular Atlas · Generated by wolfram-variant-card skill *Every assumption documented.*