MOLECULAR ATLAS · VARIANT CARD

WFS1 L445V — Wolframin

Leu→Val p445 TM4 AM=0.10 ddg=+0.32 pLDDT=84. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	L445V (p.Leucine445Valine)
DNA change	c.1333C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000349318
Amino acid change	conservative volume reduction

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 445	**84.12** HIGH CONFIDENCE
Domain	TM4 (427-447), helical transmembrane
Position context	TM4 (427-447)
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: SER446 (2.5 Å), TYR444 (2.5 Å — partner of S443R), THR442 (3.8 Å). Near S443R cluster. The Atlas's neighbor extraction surfaces this variant's contacts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.096

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.32 kcal/mol

Stabilising · Job 177992513026

PLDDT (ALPHAFOLD)

84.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status	criteria provided, conflicting classifications
Last evaluated	2025/09/02 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	L445V 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 clear from neighbor analysis. Therapeutic strategy: site-directed at the contacts identified above.

> TM4 cluster adjacent to S443R.

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