MOLECULAR ATLAS · VARIANT CARD

WFS1 V644L — Wolframin

Val→Leu p644 TM10 AM=0.10 ddg=-0.35 pLDDT=82. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	V644L (p.Valine644Leucine)
DNA change	c.1930G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215364
Amino acid change	conservative volume increase

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 644	**81.69** HIGH CONFIDENCE
Domain	TM10 (632-652), helical transmembrane
Position context	TM10 (632-652)
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: ILE643 (2.5 Å), LEU645 (2.5 Å), LEU640 (3.7 Å). Conservative TM10 substitution. The Atlas's neighbor extraction surfaces this variant's contacts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.096

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.35 kcal/mol

Destabilising · Job 177992515188

PLDDT (ALPHAFOLD)

81.69

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/07/06 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	V644L 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.

TM10 conservative variant.
