MOLECULAR ATLAS · VARIANT CARD

WFS1 L499F — Wolframin

Leucine → Phenylalanine at position 499 inside TM6. ClinVar Conflicting including monogenic diabetes + WFS1 spectrum. AlphaMissense 0.11 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.62.

IDENTITY

Variant	L499F (p.Leucine499Phenylalanine)
DNA change	c.1495C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000045436
Amino acid change	Leucine (L) → Phenylalanine (F) — branched aliphatic to aromatic. Volume increase + aromatic introduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 499	**80.62** HIGH CONFIDENCE
Domain	TM6 (496-516), helical transmembrane
Position context	TM6 (residues 496–516) · position 499 near TM6 start (pLDDT 81).
IDR flag	No — pLDDT well above 50 threshold

> Position 499 in TM6 near start. Neighbors: ASN500 (2.4 Å), VAL498 (2.5 Å), VAL491 (3.6 Å). Conservative aliphatic environment. L499F introduces aromatic volume in TM6. AM 0.11 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.106

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.62 kcal/mol

Destabilising · Job 177992509282

PLDDT (ALPHAFOLD)

80.62

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/27 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	L499F is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-Related Spectrum Disorders
- Monogenic diabetes

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 3/4 — Most Druggable (AM under-call). |ΔΔG| 0.62. AlphaMissense 0.11 below threshold but multi-phenotype confirms.

Mechanism: volume increase in TM6 start. Therapeutic: TM6 cluster (with P504L, C505Y, Y508C, V503G).

L499F extends TM6 multi-variant cluster — six variants now converge on TM6 mid-helix region.