MOLECULAR ATLAS · VARIANT CARD

WFS1 L592V — Wolframin

Leucine → Valine at position 592 inside TM9. ClinVar Conflicting. AlphaMissense 0.13 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.52. pLDDT 63 borderline.

IDENTITY

Variant	L592V (p.Leucine592Valine)
DNA change	c.1774C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001320760
Amino acid change	Leucine (L) → Valine (V) — branched aliphatic to smaller branched aliphatic. Conservative volume reduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 592	**62.62** CONFIDENT
Domain	TM9 (589-609), helical transmembrane
Position context	TM9 (residues 589–609) · position 592 (pLDDT 63 borderline).
IDR flag	No — pLDDT well above 50 threshold

> Position 592 in TM9. Neighbors: GLU593 (2.4 Å), SER591 (2.5 Å), PHE589 (4.0 Å — TM9 start). L592V conservative volume reduction in TM9. AM 0.13 under-call; Conflicting clinical evidence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.128

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.52 kcal/mol

Destabilising · Job 177992508277

PLDDT (ALPHAFOLD)

62.62

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/06/24 00:00
Inheritance	Not specified.
WFS1 variant landscape	L592V 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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Category 4 — Stable Fold, Function Disrupted (AM under-call, pLDDT borderline). |ΔΔG| 0.52. AlphaMissense 0.13 below threshold.

Mechanism: conservative TM9 volume reduction. Therapeutic: TM9 site-directed.

L592V is TM9 — same helix as P607L/P607R. TM9 cluster grows.