MOLECULAR ATLAS · VARIANT CARD

WFS1 S469L — Wolframin

Serine → Leucine at position 469 inside TM5. ClinVar Conflicting. AlphaMissense 0.18 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.14.

IDENTITY

Variant	S469L (p.Serine469Leucine)
DNA change	c.1406C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001587484
Amino acid change	Serine (S) → Leucine (L) — polar hydroxyl replaced by branched aliphatic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 469	**71.19** HIGH CONFIDENCE
Domain	TM5 (465-485), helical transmembrane
Position context	TM5 (residues 465–485) · position 469 (pLDDT 71).
IDR flag	No — pLDDT well above 50 threshold

> Position 469 in TM5 — first TM5 variant at v3 depth. Neighbors: LEU468 (2.5 Å), LEU470 (2.5 Å), GLY466 (3.8 Å). Hydrophobic TM environment. S469L removes hydroxyl from TM5 (favorable energetically), but the wild-type serine's H-bond capacity supported functional geometry. AM 0.18 under-call; Conflicting evidence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.176

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.14 kcal/mol

Destabilising · Job 177992501609

PLDDT (ALPHAFOLD)

71.19

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/10/16 00:00
Inheritance	Not specified.
WFS1 variant landscape	S469L 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). |ΔΔG| 0.14. AlphaMissense 0.18 below threshold. Limited clinical evidence.

Mechanism: lost serine H-bonding in TM5. Therapeutic: TM5 site-directed.

S469L is the first TM5 variant in the Atlas at full v3 depth — establishes TM5 as a target.