MOLECULAR ATLAS · VARIANT CARD

WFS1 S430L — Wolframin

Serine → Leucine at position 430 inside TM4. ClinVar Conflicting including Wolfram syndrome 1. AlphaMissense 0.932, ΔΔG -0.01 (neutral). Same position as S430W (Atlas card adjacent).

IDENTITY

Variant	S430L (p.Serine430Leucine)
DNA change	c.1289C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001484968
Amino acid change	Serine (S) → Leucine (L) — small polar hydroxyl replaced by branched aliphatic hydrophobic. Loss of H-bond capacity; modest volume increase.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 430	**89.75** HIGH CONFIDENCE
Domain	TM4 (427-447), helical transmembrane
Position context	TM4 (residues 427–447) · position 430 near TM4 start (pLDDT 90). Same position as S430W.
IDR flag	No — pLDDT well above 50 threshold

> Position 430 sits in TM4 with the E431 hub contact. Same neighbors as S430W: CYS429 (2.5 Å), GLU431 (2.5 Å — E431 hub), SER551 (4.0 Å — TM4-TM7 cross-helix), PRO428 (4.1 Å), ALA433 (4.4 Å). S430L is the second substitution at position 430 (with S430W). Where S430W introduced massive aromatic volume, S430L introduces conservative aliphatic volume. The H-bond between S430's hydroxyl and E431's carboxylate is lost in both — same mechanism. The near-zero ΔΔG indicates fold easily accommodates the more conservative leucine. AlphaMissense 0.932 + Wolfram 1 confirm severe functional consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.932

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.01 kcal/mol

Destabilising · Job 177992300983

PLDDT (ALPHAFOLD)

89.75

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/07/24 00:00
Inheritance	Wolfram syndrome 1 documented (conflicting classifications).
WFS1 variant landscape	S430L is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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. ΔΔG ≈ 0 — fold unchanged. AlphaMissense 0.932 confirms severe functional consequence.

Mechanism: loss of S430-E431 H-bond. Therapeutic: same E431 hub target as S430W.

S430L + S430W at same position — both pathogenic, both targeting E431 hub. Drug discovery at E431 has now 6+ convergent variant targets.