MOLECULAR ATLAS · VARIANT CARD

# WFS1 S430W — Wolframin

Serine → Tryptophan at position 430 inside TM4. ClinVar Likely pathogenic. AlphaMissense 0.979, DynaMut2 ΔΔG -0.74 kcal/mol (destabilising). A massive volume increase in a TM helix.

## IDENTITY

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|---|---|
| Variant | S430W (p.Serine430Tryptophan) |
| DNA change | c.1289C>G |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV001297548 |
| Amino acid change | Serine (S) → Tryptophan (W) — small polar hydroxyl replaced by bulky aromatic indole. Roughly four-fold side-chain volume increase plus aromatic π-system added. |

## STRUCTURAL CONTEXT

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|---|---|
| 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 the start of TM4 (pLDDT 90). |
| IDR flag | No — pLDDT well above 50 threshold |

Position 430 sits near the start of TM4. The AlphaFold model places S430 within 5 Å of CYS429 (2.5 Å), GLU431 (2.5 Å — same E431 contacted by A559D and P428R), SER551 (4.0 Å — TM4-TM7 cross-helix), PRO428 (4.1 Å), and ALA433 (4.4 Å). The E431 contact at 2.5 Å is structurally significant — the wild-type serine's hydroxyl likely H-bonds to E431's carboxylate. Replacing serine with tryptophan introduces a massive volume increase. The pocket sized for serine cannot accommodate tryptophan without substantial rearrangement. The H-bond to E431 is lost (tryptophan's indole is aromatic, not H-bond-donating in this geometry). The cross-helix contact to S551 in TM7 is perturbed. The |ΔΔG| of 0.74 reflects fold absorption at meaningful cost. AlphaMissense's 0.979 confirms severe functional consequence.

## COMPUTATIONAL PREDICTIONS

| ALPHAMISSENSE | DYNAMUT2 ΔΔG | PLDDT (ALPHAFOLD) |
|---|---|---|
| **0.979** | **-0.74** kcal/mol | **89.75** |
| am_class: **LPath** — threshold > 0.564 | Destabilising · Job 177991411668 | high confidence |

## CLINICAL EVIDENCE

| | |
|---|---|
| ClinVar classification | **LIKELY PATHOGENIC** |
| Review status | no assertion criteria provided |
| Last evaluated | 1/01/01 00:00 |
| Inheritance | Inheritance not specified. ClinVar Likely pathogenic. |
| WFS1 variant landscape | S430W is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- (no specific conditions catalogued for S430W)

## 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| = 0.74 kcal/mol — fold survives. AlphaMissense 0.979 confirms severe functional consequence.

The mechanism is volume mismatch in TM4 plus loss of the S430-E431 H-bond. Therapeutic strategy: site-directed at the E431 microregion (also touched by A559D and P428R).

S430W is the fourth Atlas variant contacting E431 (with A559D, P428R, E431Q in the next card). E431 emerges as a hub residue in the WFS1 lumenal-membrane interface — multiple pathogenic variants converge on it.