MOLECULAR ATLAS · VARIANT CARD

WFS1 P292S — Wolframin

Proline → Serine at position 292 in wolframin's N-terminal cytoplasmic domain. ClinVar Likely pathogenic for classical Wolfram syndrome 1. AlphaMissense 0.957, DynaMut2 ΔΔG -0.74 kcal/mol (destabilising). Critically, pLDDT at this position is 54 — just above the Category 5 IDR threshold but in a low-confidence region.

IDENTITY

Variant	P292S (p.Proline292Serine)
DNA change	c.874C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003377398
Amino acid change	Proline (P) → Serine (S) — a rigid, helix-breaking residue replaced by a small polar hydroxyl-bearing residue. The substitution removes the proline's backbone constraint and introduces hydrogen-bonding capacity.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 292	**54.16** CONFIDENT
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 292 sits in a region with relatively low AlphaFold confidence (pLDDT 54), just above the Cat 5 IDR threshold of 50. Interpret structural predictions here with caution.
IDR flag	No — pLDDT well above 50 threshold

Position 292 sits in wolframin's N-terminal cytoplasmic domain. The AlphaFold model places P292 within 5 Å of LEU293 (2.5 Å), TYR291 (2.5 Å), VAL288 (3.6 Å), HIS294 (4.4 Å), and ALA295 (4.7 Å). The local environment is mixed hydrophobic-polar. The wild-type proline at 292 likely plays a deliberate structural role — proline residues in cytoplasmic domains often define loop boundaries or contribute backbone constraints that orient the domain for partner binding. Replacing it with serine removes that backbone constraint and adds a hydroxyl group with H-bond capacity. The |ΔΔG| of 0.74 kcal/mol is interpretively complicated by the pLDDT of 54. DynaMut2

assumes a meaningful input structure; at pLDDT 54 the local AlphaFold prediction has lower confidence than the typical Atlas variant. The ΔΔG should be read as a directional indicator rather than a quantitative claim. AlphaMissense's 0.957 score is independently supportive — the substitution is pathogenic even if the structural mechanism is partially obscured by model uncertainty. ClinVar Likely Pathogenic for classical Wolfram syndrome 1 confirms the variant's clinical relevance.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.957	**-0.74** kcal/mol	**54.16**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991929544	confident

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2022/03/31 00:00
Inheritance	Autosomal recessive Wolfram syndrome 1 phenotype documented in ClinVar.
WFS1 variant landscape	P292S 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 (with caveat). |ΔΔG| = 0.74 kcal/mol below the fold-integrity threshold. AlphaMissense 0.957 confirms pathogenic signal. However, pLDDT of 54 means the structural details deserve

experimental validation before drug design proceeds.

The mechanism is removal of a deliberate proline backbone constraint plus introduction of a polar hydroxyl. Therapeutic strategy: a small molecule that stabilizes the wild-type backbone geometry around the position 292 loop region. Pharmacological chaperone screening is the safer initial approach given the structural confidence caveat.

P292S sits in a borderline-confidence region of the AlphaFold model. The Atlas captures this with the pLDDT score; pre-atlas drug discovery would have either treated the variant at full structural confidence (overconfident) or ignored it entirely (under-utilizing the AlphaMissense signal). The dual-metric framing makes the appropriate caution visible — proceed with chaperone screening, validate experimentally, then proceed to docking once the structural geometry is confirmed.
