MOLECULAR ATLAS · VARIANT CARD

WFS1 P724S — Wolframin

Proline → Serine at position 724 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic/Likely pathogenic for Wolfram syndrome 1. AlphaMissense 0.889, DynaMut2 ΔΔG -0.81 kcal/mol (destabilising). A proline-removal variant — companion to the L723P variant at the immediately preceding position.

IDENTITY

Variant	P724S (p.Proline724Serine)
DNA change	c.2170C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000379865
Amino acid change	Proline (P) → Serine (S) — rigid helix-breaking residue replaced by small polar hydroxyl-bearing residue. Removes backbone constraint; adds H-bond capacity.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 724	**89.25** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 724 in the ER lumen (pLDDT 89).
IDR flag	No — pLDDT well above 50 threshold

Position 724 sits in wolframin's C-terminal lumenal domain, immediately downstream of L723 (see L723P Atlas card). The AlphaFold model places P724 within 5 Å of LEU723 (2.5 Å — partner of L723P), PHE725 (2.5 Å), PHE726 (4.6 Å), and ILE727 (5.0 Å). The local environment is hydrophobic-rich (L723, F725, F726, I727). The wild-type proline at 724 defines the backbone geometry of the L723-P724 sequence transition. Removing the proline (P724S) eliminates that controlled kink, freeing the backbone to adopt a more linear conformation. Combined with L723P (Atlas card adjacent), which introduces a proline at L723, the two variants together show how either side of the wild-type Leu-Pro motif can be perturbed to produce pathogenic outcome. The new S724 introduces a polar hydroxyl into a hydrophobic environment — energetically unfavorable. The |ΔΔG| of 0.81 reflects this combined cost: lost backbone geometry plus introduced polarity.

AlphaMissense's 0.889 plus Wolfram syndrome 1 clinical evidence confirm pathogenic mechanism.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.889

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.81 kcal/mol

Destabilising · Job 177991405609

PLDDT (ALPHAFOLD)

89.25

high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2026/01/26 00:00
Inheritance	Wolfram syndrome 1 (AR) documented.
WFS1 variant landscape	P724S 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| = 0.81 kcal/mol — fold survives. AlphaMissense 0.889 confirms severe functional consequence.

The mechanism is loss of the wild-type Leu-Pro backbone geometry at the 723-724 transition, plus introduction of polarity into a hydrophobic environment. Therapeutic strategy: site-directed at the L723-P724-F725

microregion. Drug discovery here has two convergent variants (L723P and P724S).

P724S is the proline-removal complement to L723P — both at the same wild-type Leu-Pro motif, both pathogenic. The Atlas captures both as therapeutic targets at the same backbone microregion.
