MOLECULAR ATLAS · VARIANT CARD

WFS1 P724L — Wolframin

Proline → Leucine at position 724 in lumenal domain. ClinVar Conflicting. AlphaMissense 0.906, ΔΔG -0.24. Same position as P724S (Atlas card adjacent) — proline-removal pair.

IDENTITY

Variant	P724L (p.Proline724Leucine)
DNA change	c.2171C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000004509
Amino acid change	Proline (P) → Leucine (L) — rigid helix-breaking replaced by branched aliphatic. Removes backbone constraint.

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 (pLDDT 89). Same as P724S.
IDR flag	No — pLDDT well above 50 threshold

> Position 724 same neighbors as P724S: LEU723 (2.5 Å — partner of L723P), PHE725 (2.5 Å), PHE726 (4.6 Å), ILE727 (5.0 Å). P724L is the second substitution at 724 (with P724S). Where P724S added polarity into hydrophobic environment, P724L is conservative hydrophobic-to-hydrophobic. Both lose the backbone kink. Combined with L723P, three Atlas variants converge on the 723-724 Leu-Pro motif. |ΔΔG| 0.24 + AlphaMissense 0.906 confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.906		89.25

am_class: **LPath** — threshold > 0.564	**-0.24** kcal/mol Destabilising · Job 177992458146	high confidence

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CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2024/11/05 00:00
Inheritance	Not specified.
WFS1 variant landscape	P724L 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 3/4 — Most Druggable. |ΔΔG| = 0.24 — fold survives. AlphaMissense 0.906 confirms severe consequence.

Mechanism: loss of wild-type Leu-Pro backbone geometry. Therapeutic: same target as L723P, P724S.

P724L + P724S + L723P all converge on the 723-724 backbone microregion — three convergent variant targets.
