MOLECULAR ATLAS · VARIANT CARD

WFS1 L723P — Wolframin

Leucine → Proline at position 723 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic. AlphaMissense 0.959, DynaMut2 ΔΔG -0.19 kcal/mol (destabilising). Another proline-introduction variant in the lumenal fold.

IDENTITY

Variant	L723P (p.Leucine723Proline)
DNA change	c.2168T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002203530
Amino acid change	Leucine (L) → Proline (P) — flexible branched hydrophobic replaced by rigid helix-breaking residue. Same proline-introduction mechanism class as L543P, L402P, L804P.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 723	**82.69** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 723 in the ER lumen (pLDDT 83).
IDR flag	No — pLDDT well above 50 threshold

Position 723 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places L723 within 5 Å of MET722 (2.5 Å), PRO724 (2.5 Å), ILE720 (3.6 Å), ASN721 (4.6 Å), and ALA719 (4.8 Å). The local environment is hydrophobic-rich (M722, I720, A719) with a single polar residue (N721). Notably, PRO724 sits at 2.5 Å — the immediate downstream neighbor is already a proline. Replacing L723 with proline introduces a second proline immediately adjacent to the existing P724 — a Pro-Pro motif is unusual and structurally distinctive. Two adjacent prolines create a particularly rigid backbone segment with restricted conformational options. The wild-type Leu-Pro motif at 723-724 transitions from flexible to constrained backbone; the variant Pro-Pro motif is constrained on both sides. The |ΔΔG| of 0.19 is modest — the fold absorbs the new proline because the local environment was already constrained. But the geometry shifts: the Pro-Pro motif likely adopts a different local conformation than the wild-type Leu-Pro, and

surrounding residues (M722, I720) rearrange to accommodate. AlphaMissense's 0.959 score captures the functional severity — the shifted local geometry disrupts whatever interaction the wild-type Leu-Pro motif enabled.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.959	**-0.19** kcal/mol	**82.69**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990271493	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/12/16 00:00
Inheritance	Inheritance not specified. ClinVar Pathogenic.
WFS1 variant landscape	L723P is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for L723P — ClinVar Pathogenic by review evidence)

RESEARCH PATH DECISION TREE

```
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
```

Category 3/4 — Most Druggable. |ΔΔG| = 0.19 kcal/mol — fold essentially unperturbed. AlphaMissense 0.959 confirms pathogenic mechanism is functional rather than structural.

The mechanism is creation of an unusual Pro-Pro motif at positions 723-724, shifting the local backbone geometry from a Leu-Pro transition to a rigid Pro-

Pro segment. Therapeutic strategy: site-directed small molecules at the position 720-724 region, ideally compensating for the geometric shift.

This is one of several proline-introduction variants in the Atlas (L402P, L543P, L723P, L804P). The therapeutic vocabulary across this class is consistent: stabilize local backbone geometry against the introduced proline kink.

L723P creates a Pro-Pro motif rare in folded proteins. The Atlas's neighbor analysis surfaces this directly — PRO724 at 2.5 Å is the next-residue neighbor. The unusual geometry of two adjacent prolines is what distinguishes L723P's mechanism from other proline-introduction variants in the Atlas.
