MOLECULAR ATLAS · VARIANT CARD

WFS1 L672P — Wolframin

Leucine → Proline at position 672 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic. AlphaMissense 0.947, DynaMut2 ΔΔG -0.28 kcal/mol (destabilising). A proline-introduction variant adjacent to C673 (the cysteine partner in the C690R disulfide discussion).

IDENTITY

Variant	L672P (p.Leucine672Proline)
DNA change	c.2015T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000918069
Amino acid change	Leucine (L) → Proline (P) — flexible branched hydrophobic replaced by rigid helix-breaking residue.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 672	**87.69** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 672 in the ER lumen (pLDDT 88).
IDR flag	No — pLDDT well above 50 threshold

> Position 672 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places L672 within 5 Å of CYS673 (2.4 Å — same C673 discussed in C690R/C690Y Atlas cards for the inferred disulfide), ALA671 (2.5 Å), TYR669 (3.8 Å — partner of Y669C/Y669H), GLN668 (4.1 Å), and ALA677 (4.5 Å). The wild-type leucine at 672 contributes hydrophobic packing in a region densely populated by structurally important residues: C673 (potential disulfide), Y669 (aromatic packing partner), Q668. Replacing it with proline introduces a backbone kink that perturbs the geometry of this multi-residue contact cluster. The |ΔΔG| of 0.28 reflects fold accommodation. AlphaMissense's 0.947 confirms severe functional consequence. The mechanism is geometric — backbone kink propagates through the C673-Y669-Q668 microregion.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.947 am_class: **LPath** — threshold > 0.564	**-0.28** kcal/mol Destabilising · Job 177991930402	**87.69** high confidence

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CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2025/07/24 00:00
Inheritance	Inheritance not specified.
WFS1 variant landscape	L672P 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| = 0.28 — fold survives. AlphaMissense 0.947 confirms severe functional consequence.

Mechanism is proline-induced backbone kink near the C673-Y669 microregion (shared with Y669C, Y669H, C690R, C690Y atlas cards). Therapeutic strategy: site-directed at this dense contact cluster.

L672P sits adjacent to the C673-Y669-C690 cluster — one of the densest variant-target hubs in the Atlas. Multiple variants converge here, all with site-directed rescue opportunities.