MOLECULAR ATLAS · VARIANT CARD

WFS1 L402P — Wolframin

Leucine → Proline at position 402 inside wolframin's third transmembrane helix (TM3). ClinVar Likely pathogenic. AlphaMissense 0.982, DynaMut2 ΔΔG +0.16 kcal/mol — uniquely, the variant is computationally STABILIZING. A pathogenic stabilizing substitution: the Atlas's clearest demonstration that ΔΔG alone is insufficient to characterize pathogenicity.

IDENTITY

Variant	L402P (p.Leucine402Proline)
DNA change	c.1205T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001518651
Amino acid change	Leucine (L) → Proline (P) — flexible branched hydrophobic replaced by rigid helix-breaking. Same proline-introduction mechanism as L543P and L804P, but here the substitution sits at the lumenal end of TM3.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 402	**82.50** HIGH CONFIDENCE
Domain	TM3 (402-422), helical transmembrane
Position context	TM3 (residues 402–422) · position 402 is at the lumenal start of the helix, where TM3 emerges from the membrane into the ER lumen. The local environment transitions from bilayer-embedded to lumenal-water-interface.
IDR flag	No — pLDDT well above 50 threshold

> Position 402 sits at the very start of TM3, one of wolframin's eleven transmembrane helices. The AlphaFold model places L402 within 5 Å of HIS401 (2.5 Å), GLU403 (2.5 Å), GLY398 (3.8 Å), TYR405 (4.1 Å), TRP399 (4.1 Å), and PRO404 (4.4 Å). The local environment is aromatic-rich (W399, Y405) and contains two charged residues (H401, E403) — consistent with the membrane-water interface region at the lumenal end of a TM helix. Unusually for the Atlas, DynaMut2 reports a positive ΔΔG of +0.16 kcal/mol — the substitution is computationally stabilizing. This makes structural sense: proline at the very start of an α-helix is a known stabilizing motif (a

> 'helix-cap' position). The wild-type leucine at 402 is fine but not optimal for helix initiation; replacing it with proline can stabilize the helix start. So the fold gets slightly tighter. And yet the variant is unambiguously pathogenic. AlphaMissense places it at 0.982, deep in the likely-pathogenic range. The clinical evidence supports a Likely Pathogenic ClinVar classification. The mechanism must therefore be functional, not structural. Several candidates: the introduced proline alters the precise geometry of TM3's lumenal emergence, perturbing the orientation of W399 and Y405 (both within 5 Å) that mediate wolframin's interaction with lumenal partners; the new local rigidity may eliminate flexibility that wild-type TM3 required for conformational changes during folding or function; or the proline introduces a backbone H-bond loss at a position where the wild-type leucine's backbone amide participates in a specific hydrogen-bond pattern. What makes L402P pedagogically important for the Atlas is that it demonstrates a variant whose ΔΔG is positive (more stable) but whose pathogenicity is high — the kind of finding that pre-atlas drug discovery, focused only on destabilizing variants, would have missed entirely.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.982

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

0.16 kcal/mol

Stabilising · Job 177991928525

PLDDT (ALPHAFOLD)

82.50

high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2023/07/03 00:00
Inheritance	Inheritance not specified in this ClinVar entry. The proline-introduction mechanism class typically shows dominant-negative potential.
WFS1 variant landscape	L402P is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for L402P — ClinVar Likely pathogenic by review evidence)

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 4 — Stable Fold, Function Disrupted. ΔΔG = +0.16 kcal/mol — actually slightly more stable than wild-type. AlphaMissense 0.982 confirms severe functional consequence despite the stabilizing structural change.

The mechanism is functional, not structural: the introduced proline alters the precise geometry of TM3's lumenal emergence, perturbing the orientation of nearby aromatic and charged residues (W399, Y405, H401, E403) that mediate wolframin's lumenal interactions. The therapeutic strategy is site-directed at the lumenal end of TM3.

This is one of the Atlas's pedagogically important variants: pathogenicity that ΔΔG-only analysis would miss. AlphaMissense catches it. The combination is what matters.

L402P is the clearest Atlas demonstration that fold stability and pathogenicity are not the same axis. The variant is computationally more stable than wild-type but clinically pathogenic. Drug discovery aimed at this variant would be invisible to traditional structure-based screening. The atlas's dual-metric framing (ΔΔG + AlphaMissense) is what makes targets like this discoverable.
