MOLECULAR ATLAS · VARIANT CARD

WFS1 L543P — Wolframin

Leucine → Proline at position 543 inside wolframin's seventh transmembrane helix (TM7). ClinVar Likely pathogenic. AlphaMissense 0.993, DynaMut2 ΔΔG -0.34 kcal/mol (destabilising). A proline-into-TM-helix variant — a structurally severe class of substitution.

IDENTITY

Variant	L543P (p.Leucine543Proline)
DNA change	c.1628T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002846082
Amino acid change	Leucine (L) → Proline (P) — a flexible, branched hydrophobic residue replaced by a rigid, ring-locked, helix-breaking residue. The reverse of P504L's chemistry: where P504L removed a deliberate helix kink, L543P introduces an unintended one.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 543	**90.94** HIGH CONFIDENCE
Domain	TM7 (529-549), helical transmembrane
Position context	TM7 (residues 529–549) · position 543 is bilayer-embedded near the middle of the helix, where the helix integrity is most critical for membrane spanning.
IDR flag	No — pLDDT well above 50 threshold

Position 543 sits in the middle of TM7, one of wolframin's eleven transmembrane helices. The AlphaFold model places L543 within 5 Å of GLU542 (2.5 Å), SER544 (2.5 Å), MET539 (3.7 Å), TRP540 (3.9 Å), PHE881 (4.1 Å, from TM11 — TM7-TM11 cross-helix contact), and CYS541 (4.3 Å). The wild-type leucine fits cleanly into this position, contributing branched hydrophobic packing into TM7's helical structure and into the TM7-TM11 helix-helix interface. Replacing leucine with proline in the middle of a transmembrane helix is one of the more disruptive substitutions in protein chemistry. Proline's backbone is locked into a five-membered ring; its phi angle is constrained to roughly -60°; it cannot serve as a hydrogen-bond

donor in the backbone amide network that holds α-helices together. When proline is introduced into the middle of a helix, the helix either kinks at that position or partially unwinds — neither outcome is consistent with the wild-type membrane-spanning geometry. DynaMut2 returns a modest |ΔΔG| of 0.34 kcal/mol. This understates the structural cost. The model captures local rearrangement but does not fully simulate the consequence of breaking an α-helix in the middle of a bilayer-spanning segment: TM7's ability to traverse the membrane in its wild-type orientation is compromised, and the lost packing against PHE881 in TM11 perturbs the relative geometry of two helices simultaneously. AlphaMissense's score of 0.993 captures this severity. The variant is pathogenic by mechanism — broken TM7 geometry, disrupted TM7-TM11 interface — rather than by global misfolding.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.993	**-0.34** kcal/mol	**90.94**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991411187	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2023/03/15 00:00
Inheritance	Inheritance not specified in this ClinVar entry. The mechanistic profile (broken TM helix geometry) suggests a dominant-negative potential, consistent with the AD-leaning WFS1 spectrum.
WFS1 variant landscape	L543P is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for L543P — 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 3/4 — Most Druggable. |ΔΔG| = 0.34 kcal/mol — fold absorbs the proline introduction. AlphaMissense 0.993 confirms severe functional consequence.

The mechanism is helix integrity disruption inside TM7 plus loss of the TM7-TM11 cross-helix packing at the PHE881 contact. This is the same TM-TM interface vocabulary used elsewhere in the Atlas (TM3-TM10 at PHE414, TM6-TM11 at PRO885) but with proline-induced helix breakage as the perturbation mechanism rather than charge or volume mismatch.

Therapeutic strategy: a small molecule that stabilizes TM7's helical register through the position 542-544 region, ideally engaging both TM7 and TM11 across the helix interface. Pharmacological chaperone screening with a focus on TM helix stabilization is a plausible secondary track.

L543P is one of four proline-introduction-or-removal variants in this batch (L402P, L543P, L804P, P504L). Across these variants, the structural cost is qualitatively different from typical AA swaps — the protein either gains or loses a deliberate backbone kink. Drug discovery for this class targets local helix geometry rather than specific binding pockets. The Atlas's structural framework makes this whole class visible as a coherent therapeutic target category.