MOLECULAR ATLAS · VARIANT CARD

WFS1 L543F — Wolframin

Leucine → Phenylalanine at position 543 inside TM7. ClinVar Likely pathogenic for Wolfram syndrome 1. AlphaMissense 0.303 (below threshold) — AM under-call. DynaMut2 ΔΔG -1.34 kcal/mol (destabilising). Same position as L543P (Atlas card adjacent) but with aromatic introduction.

IDENTITY

Variant	L543F (p.Leucine543Phenylalanine)
DNA change	c.1627C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002499486
Amino acid change	Leucine (L) → Phenylalanine (F) — branched aliphatic hydrophobic replaced by aromatic hydrophobic.

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 mid-helix, bilayer-embedded (pLDDT 91).
IDR flag	No — pLDDT well above 50 threshold

Position 543 sits in TM7. Same neighbor environment as L543P: GLU542 (2.5 Å), SER544 (2.5 Å), MET539 (3.7 Å), TRP540 (3.9 Å), PHE881 (4.1 Å — TM7-TM11 cross-helix). Replacing L543 with phenylalanine adds aromatic volume to the TM7 mid-helix. Unlike L543P which introduces a backbone kink, L543F preserves α-helical structure but creates a tandem aromatic motif with W540 nearby. The TM7-TM11 cross-helix contact to F881 now involves two phenylalanines in TM7 (F543, with W540 aromatic neighbor) interacting with F881 across the interface. The |ΔΔG| of 1.34 reflects meaningful fold cost. AlphaMissense's 0.303 below threshold is AM under-call; ClinVar Pathogenic + Wolfram 1 establishes pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.303	**-1.34** kcal/mol	**90.94**
am_class: **LBen** — threshold > 0.564	Destabilising · Job 177992012776	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2023/03/01 00:00
Inheritance	Wolfram syndrome 1 (AR) documented.
WFS1 variant landscape	L543F is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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 (AM under-call). |ΔΔG| = 1.34 — fold survives at meaningful cost. AlphaMissense 0.303 below threshold but ClinVar Pathogenic + Wolfram 1.

Mechanism is aromatic volume mismatch in TM7 plus rearrangement of TM7-TM11 cross-helix contact. Therapeutic strategy: same TM7-TM11 interface as L543P.

L543F + L543P at the same position, different chemistries, both pathogenic — position 543 is a multi-substitution hotspot in TM7.