MOLECULAR ATLAS · PILOT VARIANT CARD

WFS1 L543R — Wolframin

Arginine for leucine at position 543. A permanent positive charge forced into the lipid bilayer interior — and R558's structural neighbor in transmembrane helix 7.

IDENTITY

Variant	L543R (p.Leucine543Arginine)
DNA change	c.1628T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002203523
Amino acid change	Leucine (L, hydrophobic, branched, classic lipid-bilayer-friendly side chain) → Arginine (R, large, positively charged, hydrophilic, guanidinium-bearing)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6 (released Aug 2025)
pLDDT at residue 543	**90.94** HIGH CONFIDENCE
Domain	TM7 (529-549), helical transmembrane
Position context	Inside transmembrane helix 7 (529–549), 6 residues upstream of where R558 anchors at TM7's cytoplasmic end
IDR flag	No — pLDDT well above 50 threshold

TM7 is one of wolframin's eleven membrane-spanning helices, sitting fully inside the ER lipid bilayer. Leucine is exactly the kind of residue you expect there — uncharged, hydrophobic, content with greasy company. Arginine is the opposite — a large, permanently-positively-charged guanidinium group that is thermodynamically expensive to drag through a lipid bilayer. The single substitution puts a charge inside the membrane core. First-principles biochemistry says this should be severely destabilizing. The measurement says the helix accommodates it, likely because nearby polar residues in TM7 provide partial compensation.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.969

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-1.75 kcal/mol

Destabilising · Job 177985958201

PLDDT (ALPHAFOLD)

90.94

high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2026/02/01
Inheritance	Both autosomal dominant and autosomal recessive forms documented
WFS1 variant landscape	L543R is 1 of 326 pathogenic-spectrum variants in WFS1 (out of 2,243 catalogued in ClinVar)

- Wolfram syndrome 1
- Wolfram-like syndrome
- Autosomal dominant nonsyndromic hearing loss 6
- Type 2 diabetes mellitus
- Cataract 41

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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Final classification: Category 2/3 — Most Druggable. The largest ΔΔG magnitude of the pilot set, but still under the Cat 2 boundary. DynaMut2 ΔΔG = −1.75 kcal/mol. The TM helix accommodates the charged side chain better than expected, but the destabilization is real and the largest signal of the five pilot variants. This makes L543R the highest-yield candidate for pharmacological chaperone screening — the variant most

likely to respond to a small molecule that stabilizes TM7's hydrophobic packing.

Why this card tells the structural-neighbor story. L543 and R558 sit on the same transmembrane helix, six residues apart. The Mol* viewer shows both positions in TM7 when you rotate it. Two pathogenic variants, one helix, one shared therapeutic target. A small molecule designed to stabilize TM7 — the membrane-anchoring spine of wolframin — could in principle rescue both. The Atlas captures local pathogenic clusters that linear ClinVar scrolling would miss.
