MOLECULAR ATLAS · VARIANT CARD

WFS1 S443R — Wolframin

Serine → Arginine at position 443 inside wolframin's fourth transmembrane helix (TM4). ClinVar Pathogenic/Likely pathogenic. AlphaMissense 0.999 (near-maximum pathogenicity score), DynaMut2 ΔΔG -0.31 kcal/mol (destabilising). A pathogenic variant whose mechanism is charge-into-membrane disruption.

IDENTITY

Variant	S443R (p.Serine443Arginine)
DNA change	c.1329C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001315675
Amino acid change	Serine (S) → Arginine (R) — a small polar hydroxyl-bearing residue replaced by a large, positively-charged residue with a long alkyl chain and a guanidinium group (the strongest hydrogen-bond donor in the amino acid alphabet).

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 443	**88.19** HIGH CONFIDENCE
Domain	TM4 (427-447), helical transmembrane
Position context	TM4 (residues 427–447) · position 443 is bilayer-embedded near the lumenal end of the helix. The lipid environment penalizes charged side chains heavily.
IDR flag	No — pLDDT well above 50 threshold

Position 443 sits inside TM4, one of wolframin's eleven transmembrane helices. The AlphaFold model places S443 within 5 Å of THR442 (2.5 Å) and TYR444 (2.5 Å), and into a packed environment with PHE439 (3.5 Å), SER446 (3.6 Å), PHE365 (3.7 Å, from TM3), and THR440 (3.9 Å). The wild-type serine's small polar hydroxyl fits well in this membrane-embedded context, possibly forming a hydrogen bond with SER446 or with the backbone carbonyl of a nearby residue. Replacing serine with arginine here introduces three layered structural costs. First, the volume difference: arginine is one of the larger amino acids by side-chain volume, while serine is among the smaller. The local packing has to accommodate roughly four-fold more side-

chain mass. Second, the charge: arginine's guanidinium group carries a positive charge that is thermodynamically penalized in the bilayer hydrophobic core. Third, the H-bonding capacity changes — the lost serine hydroxyl is replaced by the guanidinium's strong H-bond donor character, which would prefer to engage water or polar partners outside the membrane. DynaMut2's |ΔΔG| of 0.31 kcal/mol underestimates the structural disruption. The variant probably forces local rearrangement: the arginine side chain extends toward the membrane-water interface (where its charge can be partially satisfied), pulling nearby residues out of their wild-type positions. The PHE365 contact from TM3 (3.7 Å) is particularly important — that's a helix-helix interaction, and disrupting it perturbs the relative geometry of TM3 and TM4. AlphaMissense's score of 0.999 reflects the severity of this mechanism even with a small structural ΔΔG. The variant is pathogenic because it disrupts helix-helix packing in the membrane, not because it unfolds the protein.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.999	**-0.31** kcal/mol	**88.19**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990909658	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/07/13 00:00
Inheritance	Inheritance not specified in this ClinVar entry. Given the multiple submitters with consistent Pathogenic/Likely pathogenic classification, the variant likely contributes to the WFS1 spectrum across both AR and AD presentations.
WFS1 variant landscape	S443R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for S443R — ClinVar Pathogenic/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| = 0.31 kcal/mol — fold survives. AlphaMissense 0.999 (near-maximum) confirms severe functional consequence despite modest structural cost.

The mechanism is charge-into-membrane plus TM3-TM4 helix-helix interface disruption. S443R is one of several Atlas variants where a charged residue is introduced into a bilayer-embedded position (compare T641K, V536E). Across these cases, the therapeutic target is the helix-helix interface that the wild-type residue stabilized, not the helix itself.

The therapeutic strategy is site-specific: a small molecule that occupies the TM3-TM4 interface near the PHE365 contact would compensate for the disrupted packing. The atlas-derived structural framework makes this target geometry visible — pre-atlas, the small ΔΔG would have deprioritized this variant for structure-based drug design.

S443R is the cleanest example in the Atlas of the "charge-into-membrane" mechanism class. The protein folds, the variant is pathogenic, and the mechanism is helix-helix interface disruption inside the bilayer. Drug discovery for this class of variant targets the TM-TM interface, not the individual TM helix. The Atlas surfaces this whole class by surfacing the cross-helix neighbor contacts in the PDB analysis.