MOLECULAR ATLAS · VARIANT CARD

WFS1 G437R — Wolframin

Glycine → Arginine at position 437 inside wolframin's fourth transmembrane helix (TM4). ClinVar Pathogenic/Likely pathogenic for Wolfram syndrome 1. AlphaMissense 0.935, DynaMut2 ΔΔG -0.59 kcal/mol (destabilising). Glycine-removal in a TM helix — a structurally severe variant class.

IDENTITY

Variant	G437R (p.Glycine437Arginine)
DNA change	c.1309G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001199427
Amino acid change	Glycine (G) → Arginine (R) — smallest amino acid replaced by large positively-charged guanidinium-bearing residue. Maximum chemistry contrast in a bilayer-embedded context.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 437	**90.31** HIGH CONFIDENCE
Domain	TM4 (427-447), helical transmembrane
Position context	TM4 (residues 427–447) · position 437 is in the middle of TM4, bilayer-embedded (pLDDT 90).
IDR flag	No — pLDDT well above 50 threshold

Position 437 sits inside TM4. The AlphaFold model places G437 within 5 Å of THR436 (2.5 Å), PHE438 (2.5 Å), ALA433 (3.7 Å), SER544 (3.8 Å — TM4-TM7 cross-helix contact), and VAL434 (3.8 Å). The SER544 contact is structurally significant: a residue from TM7 sits within 5 Å of TM4's G437, indicating helix-helix packing through this region. Glycines in transmembrane helices serve specific structural roles — often as flex points permitting helix kinks or as small residues enabling tight helix-helix packing. The G437 position appears to be the second case: it's small enough to allow TM4 and TM7 to approach closely at the S544 contact. Replacing glycine with arginine here introduces both a positive charge and substantial side-chain volume into a bilayer-embedded helix-helix interface. The TM4-TM7 packing geometry is forced apart; the new R437 side chain extends toward solvent at the

membrane-water interface. The |ΔΔG| of 0.59 reflects modest energetic cost — the fold absorbs the substitution. But the helix-helix interface is materially perturbed. AlphaMissense's 0.935 + Wolfram syndrome 1 clinical evidence confirm severe functional consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.935

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.59 kcal/mol

Destabilising · Job 177991405079

PLDDT (ALPHAFOLD)

90.31

high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/08/30 00:00
Inheritance	Wolfram syndrome 1 (AR) documented.
WFS1 variant landscape	G437R 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. |ΔΔG| = 0.59 kcal/mol — fold survives. AlphaMissense 0.935 confirms severe functional consequence.

The mechanism is glycine-removal at a TM4-TM7 helix-helix interface (S544

contact at 3.8 Å) plus charge introduction into the bilayer. Therapeutic strategy: site-directed at the TM4-TM7 interface.

G437R is the second Atlas variant disrupting a TM4-related helix-helix interface (with S443R in TM4 itself). The TM4 helix appears repeatedly in the Atlas as a target — multiple variants converge on this region's contacts with neighboring helices.
