MOLECULAR ATLAS · VARIANT CARD

WFS1 W639G — Wolframin

Tryptophan → Glycine at position 639 inside wolframin's tenth transmembrane helix (TM10). ClinVar Pathogenic. AlphaMissense 0.481 (BELOW the likely-pathogenic threshold), DynaMut2 ΔΔG -1.03 kcal/mol (destabilising). A variant where the structural cost is clear but the AlphaMissense signal is unexpectedly weak.

IDENTITY

Variant	W639G (p.Tryptophan639Glycine)
DNA change	c.1915T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003720568
Amino acid change	Tryptophan (W) → Glycine (G) — bulky aromatic replaced by the smallest amino acid. Massive volume loss; aromatic character entirely eliminated.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 639	**86.50** HIGH CONFIDENCE
Domain	TM10 (632-652), helical transmembrane
Position context	TM10 (residues 632–652) · position 639 is in the middle of TM10, bilayer-embedded (pLDDT 86).
IDR flag	No — pLDDT well above 50 threshold

Position 639 sits in the middle of TM10. The AlphaFold model places W639 within 5 Å of VAL638 (2.5 Å), LEU640 (2.5 Å), ILE636 (3.6 Å), LEU635 (3.8 Å), and ALA642 (4.3 Å). The local environment is uniformly hydrophobic — an aliphatic-rich pocket where the wild-type tryptophan's bulky indole ring contributes substantial volume. Replacing tryptophan with glycine removes the indole ring entirely, leaving a small cavity in the TM10 hydrophobic core. The DynaMut2 |ΔΔG| of 1.03 captures this — the volume mismatch produces meaningful destabilization, larger than most variants in this batch. Yet AlphaMissense places this at 0.481 — below the 0.564 likely-pathogenic threshold. AM considers this variant likely benign. The discrepancy with ClinVar Pathogenic classification is striking. Two interpretations: (1) AM's training data may under-represent TM-helix variants in general, leading to

systematic under-calling of pathogenicity in this structural context; (2) The variant may be technically pathogenic in specific clinical scenarios (compound heterozygosity, specific tissue contexts) but not in the more general population-genetics sense AM is trained on. The DynaMut2 destabilization (|ΔΔG| 1.03) is real and substantial. This is a variant where ΔΔG is informative and AM is uncertain.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.481

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

-1.03 kcal/mol

Destabilising · Job 177990266823

PLDDT (ALPHAFOLD)

86.50

high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/10/03 00:00
Inheritance	Inheritance not specified.
WFS1 variant landscape	W639G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for W639G — ClinVar 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 (AM caveat). |ΔΔG| = 1.03 kcal/mol — fold absorbs the substitution at meaningful cost. AlphaMissense 0.481 is below the likely-pathogenic threshold but ClinVar Pathogenic classification is established.

The mechanism is volume loss in a TM10 hydrophobic packing pocket — the lost tryptophan indole creates a cavity that destabilizes the local membrane-embedded geometry. Therapeutic strategy: site-directed small molecules that fill the cavity left by W639, restoring the wild-type packing volume.

The unexpected AM signal mismatch is itself a finding the Atlas surfaces — variants where structural destabilization is clear but AM training under-calls pathogenicity exist, and they deserve wet-lab characterization to clarify mechanism.

W639G demonstrates the value of the Atlas's dual-metric framing in the opposite direction from variants like T361I. Where T361I has stabilising ΔΔG but high AM (functional mechanism), W639G has destabilising ΔΔG but low AM (structural mechanism not captured by AM training). The Atlas captures both — the framework is more complete than either metric alone.
