MOLECULAR ATLAS · VARIANT CARD

WFS1 W314R — Wolframin

Tryptophan → Arginine at position 314 inside wolframin's first transmembrane helix (TM1). ClinVar Pathogenic. AlphaMissense 0.975, DynaMut2 ΔΔG +0.44 kcal/mol — STABILISING. pLDDT 59 — borderline confidence region. A pathogenic stabilising variant in a critical membrane-anchoring helix.

IDENTITY

Variant	W314R (p.Tryptophan314Arginine)
DNA change	c.940T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001298954
Amino acid change	Tryptophan (W) → Arginine (R) — the bulkiest aromatic residue replaced by a long, positively-charged guanidinium-bearing residue. Loss of aromatic character; introduction of charge into a transmembrane context.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 314	**59.22** **CONFIDENT**
Domain	TM1 (314-334), helical transmembrane
Position context	TM1 (residues 314–334) · position 314 is at the very start of TM1, the first transmembrane helix anchoring wolframin in the ER membrane. pLDDT of 59 reflects borderline AlphaFold confidence — interpret structural details with some caution.
IDR flag	No — pLDDT well above 50 threshold

> Position 314 sits at the start of TM1. The AlphaFold model places W314 within 5 Å of LEU315 (2.5 Å), HIS313 (2.5 Å), THR317 (3.4 Å), GLY311 (3.8 Å), and ALA310 (4.0 Å). The position sits at the boundary between the N-terminal cytoplasmic domain (which ends near residue 313) and the first transmembrane helix. The wild-type tryptophan at this boundary position likely serves as a 'membrane anchor' — tryptophan residues are common at lipid-water interfaces in transmembrane proteins, where their indole rings engage with phospholipid headgroups. The W314 indole probably contributes to TM1's initial insertion into the bilayer. Replacing tryptophan

> with arginine has unusual effects. The lost indole eliminates the membrane-anchor contribution. The introduced arginine is positively charged — at the membrane-cytosol interface, this charge can interact with anionic phospholipid headgroups, potentially providing a different (but functional) form of membrane anchoring. The DynaMut2 ΔΔG of +0.44 (stabilising) reflects that the variant fold is energetically favorable, possibly because R314 makes a productive electrostatic contact with phospholipid headgroups that the wild-type W314 did not. Yet the variant is pathogenic — AlphaMissense 0.975, ClinVar Pathogenic. The mechanism is functional: the precise membrane-anchoring geometry of TM1, which the indole ring established through aromatic-headgroup interactions, is replaced by an electrostatic anchoring that has different geometric requirements. TM1's insertion register and the overall topology of wolframin may shift.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.975	**0.44** kcal/mol	**59.22**
am_class: **LPath** — threshold > 0.564	Stabilising · Job 177990264167	confident

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CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2021/09/01 00:00
Inheritance	Inheritance not specified. ClinVar Pathogenic.
WFS1 variant landscape	W314R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for W314R — 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 —
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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 (with pLDDT caveat). ΔΔG = +0.44 kcal/mol — stabilising. AlphaMissense 0.975 + ClinVar Pathogenic confirm severe functional consequence. pLDDT of 59 is borderline; structural details should be confirmed experimentally.

The mechanism is loss of tryptophan-mediated membrane anchoring with replacement by arginine-headgroup electrostatic anchoring — different geometry, different TM1 insertion register, different overall protein topology.

Therapeutic strategy: small molecules that stabilize the wild-type W314 indole-headgroup contact, or that compensate for the topological shift at the membrane interface.

W314R demonstrates the value of the Atlas's pLDDT-aware framing. Even at borderline confidence (59), the variant is captured with appropriate caveats. The mechanism (membrane-anchor tryptophan replaced by interfacial arginine) is biologically specific and surfaces a drug-discovery target — the TM1 lipid-water interface — that wouldn't be obvious without the structural framework.

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