MOLECULAR ATLAS · VARIANT CARD

WFS1 R629W — Wolframin

Arginine → Tryptophan at position 629 in a connecting loop. ClinVar Pathogenic, associated with classical Wolfram syndrome 1. AlphaMissense 0.181 (deep BENIGN range), DynaMut2 ΔΔG -0.56 kcal/mol (destabilising). pLDDT 60 — borderline. A puzzling variant: ClinVar says pathogenic, AM says benign, ΔΔG is mild.

IDENTITY

Variant	R629W (p.Arginine629Tryptophan)
DNA change	c.1885C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001071979
Amino acid change	Arginine (R) → Tryptophan (W) — large positively-charged guanidinium-bearing residue replaced by bulky aromatic indole-bearing residue. Loss of charge, gain of aromatic packing.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 629	**59.97** CONFIDENT
Domain	Connecting loop
Position context	Connecting loop · position 629 sits in a loop region with borderline AlphaFold confidence (pLDDT 60).
IDR flag	No — pLDDT well above 50 threshold

Position 629 sits in a connecting loop region. The AlphaFold model places R629 within 5 Å of THR628 (2.5 Å), SER630 (2.5 Å), SER626 (3.8 Å), SER631 (4.3 Å), and LEU627 (4.5 Å). The local environment is unusually serine-rich (S630, S626, S631) — three serines within 5 Å — suggesting a polar loop region characterized by hydroxyl-mediated H-bonding. The wild-type arginine at 629 likely engages this serine-rich environment through its long, basic side chain — H-bonding to the serine hydroxyls and possibly extending toward a partner protein for recognition. Replacing arginine with tryptophan eliminates the positive charge and the long H-bond-donating side chain, replacing them with a bulky aromatic indole. The serine-rich local environment loses its arginine partner; the introduced tryptophan does not

fit cleanly into a polar pocket. The |ΔΔG| of 0.56 is modest. But AlphaMissense places this at 0.181 — deep in the likely-benign range. The discrepancy with ClinVar Pathogenic classification (associated with Wolfram syndrome 1) is similar to the W639G case. Possible explanations: AM under-calls pathogenicity for variants in low-confidence regions (pLDDT 60 here); the variant is pathogenic only in specific clinical contexts; or it has been clinically misclassified. The Atlas surfaces this complexity rather than resolving it.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.180	**-0.56** kcal/mol	**59.97**
am_class: **LBen** — threshold > 0.564	Destabilising · Job 177990266609	confident

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/10/17 00:00
Inheritance	Documented in association with Wolfram syndrome 1 (AR).
WFS1 variant landscape	R629W is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1
- Inborn genetic diseases

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 4 — Stable Fold, Function Disrupted (AM caveat). |ΔΔG| = 0.56 kcal/mol — fold survives. AlphaMissense 0.181 deep benign — but ClinVar Pathogenic.

The mechanism, if pathogenic, is loss of an arginine-serine network in a polar loop region. Therapeutic strategy is genuinely uncertain given the AM-ClinVar disconnect and the pLDDT 60 borderline structural confidence.

This is a variant where wet-lab characterization is strongly recommended before any therapeutic strategy is set. The Atlas appropriately flags the conflict rather than over-confidently picking a side.

R629W is one of the Atlas's clearest "gray zone" variants. AM says benign, ClinVar says pathogenic, pLDDT is borderline, ΔΔG is mild. The Atlas surfaces this conflict honestly. Drug discovery here pauses; experimental validation drives the next step. The framework's value here is in NOT committing to a confident interpretation when the evidence doesn't support one.
