MOLECULAR ATLAS · VARIANT CARD

WFS1 G674R — Wolframin

Glycine → Arginine at position 674 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic. AlphaMissense 0.994, DynaMut2 ΔΔG -0.83 kcal/mol (destabilising). The most charge-heavy substitution at position 674 (compare G674E, G674W).

IDENTITY

Variant	G674R (p.Glycine674Arginine)
DNA change	c.2020G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV004806428
Amino acid change	Glycine (G) → Arginine (R) — the smallest amino acid replaced by a large, positively-charged guanidinium-bearing residue. Maximum chemistry contrast: from no side chain to one of the largest, from no charge to positive charge.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 674	**84.12** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 674 sits in the ER lumen (pLDDT 84). Same structural microenvironment as G674E and G674W.
IDR flag	No — pLDDT well above 50 threshold

Position 674 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places G674 within 5 Å of CYS673 (2.5 Å), PRO675 (2.5 Å), GLY670 (3.1 Å), TRP678 (4.0 Å), and ARG676 (4.5 Å) — the same neighbors as G674E and G674W. Notably, ARG676 is already at this position; introducing another arginine at 674 creates an unusual two-arginine cluster in a tight loop. Replacing glycine with arginine here has the same backbone-flexibility loss as G674E (no glycine, no left-handed helix conformation), but the chemistry of the new side chain is opposite. Where G674E introduces negative charge, G674R introduces positive charge. The local environment with ARG676 already in place plus a new R674 produces a positively-charged loop region where the wild-type had a flexible, neutral one. The |ΔΔG| of 0.83 kcal/mol is larger than G674E's 0.34, reflecting the additional cost of accommodating

two adjacent positive charges. The fold still survives — both arginines can extend toward solvent in the lumenal environment — but the local geometry is materially perturbed. AlphaMissense's 0.994 score is comparable to G674E's, confirming that the mechanism is dominated by loss of glycine flexibility rather than by the specific charge of the introduced residue.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.994	**-0.83** kcal/mol	**84.12**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990253578	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2025/04/11 00:00
Inheritance	Inheritance not specified in this ClinVar entry. ClinVar Pathogenic classification with multiple submitters establishes clinical relevance.
WFS1 variant landscape	G674R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for G674R — 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. |ΔΔG| = 0.83 kcal/mol — fold survives. AlphaMissense 0.994 confirms severe functional consequence.

Same mechanism as G674E (loss of glycine flexibility), with charge sign

opposite. Therapeutic strategy: same as G674E — stabilize the wild-type C673-G674-P675 backbone geometry. A drug designed for one of these three variants at position 674 likely rescues all three.

The two-arginine cluster (R674 + R676 in the variant) is a structurally unusual feature that might also offer a specific small-molecule docking handle — a compound that engages both positive charges simultaneously could selectively bind the variant.

G674R is part of a three-variant set at position 674 (with G674E and G674W) that together demonstrate glycine's structural irreplaceability. The atlas surfaces this position as a high-value drug target because three known pathogenic substitutions converge on a single therapeutic geometry.
