MOLECULAR ATLAS · VARIANT CARD

WFS1 G674W — Wolframin

Glycine → Tryptophan at position 674 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic. AlphaMissense 0.991, DynaMut2 ΔΔG -0.77 kcal/mol (destabilising). The largest substitution at position 674 — backbone flexibility loss combined with massive volume increase.

IDENTITY

Variant	G674W (p.Glycine674Tryptophan)
DNA change	c.2020G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003618121
Amino acid change	Glycine (G) → Tryptophan (W) — the smallest amino acid replaced by the largest (bulky aromatic indole). Maximum volume contrast in protein chemistry.

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 in the ER lumen (pLDDT 84). Same environment as G674E, G674R.
IDR flag	No — pLDDT well above 50 threshold

Position 674 sits in wolframin's C-terminal lumenal domain, between CYS673 (2.5 Å), PRO675 (2.5 Å), GLY670 (3.1 Å), TRP678 (4.0 Å), and ARG676 (4.5 Å). The TRP678 contact at 4.0 Å is structurally significant: an existing tryptophan four residues downstream in the chain. Replacing glycine with tryptophan at position 674 has two simultaneous costs. First, the glycine backbone flexibility is gone — the local conformation must rearrange to accommodate any non-glycine residue. Second, the introduced indole ring is roughly an order of magnitude larger than glycine's missing side chain. The local pocket simply does not have space for a tryptophan in the wild-type geometry; substantial local rearrangement is forced. The combination produces a |ΔΔG| of 0.77 kcal/mol — comparable to G674R's 0.83, both larger than G674E's 0.34. The fold absorbs the substitution, but at

meaningful cost. The new W674 plus the existing W678 creates a two-tryptophan cluster in the loop, which might engage in π-stacking with each other in the variant's rearranged geometry — but this is an artifact of the mutation, not a functional feature. AlphaMissense's 0.991 score confirms severe functional consequence. The pathogenicity mechanism is the same as G674E/G674R: removal of glycine flexibility at a position that requires it, plus secondary disruption from the specific introduced residue's properties.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.991	**-0.77** kcal/mol	**84.12**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990254299	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2025/07/23 00:00
Inheritance	Inheritance not specified. ClinVar Pathogenic classification establishes clinical relevance.
WFS1 variant landscape	G674W is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for G674W — 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| = 0.77 kcal/mol — fold survives. AlphaMissense 0.991 confirms severe functional consequence.

The mechanism combines glycine flexibility loss (shared across the G674E/R/W series) with volume mismatch (specific to G674W). Therapeutic strategy: same backbone-geometry stabilization as G674E and G674R. A drug aimed at the position 674 microregion targets all three known substitutions.

The G674W variant's introduced aromatic ring could be exploited by a drug designed to displace the variant tryptophan back into a wild-type-like geometry — a selective rescue strategy that wouldn't work for G674E or G674R.

G674W completes the three-substitution series at position 674. Together with G674E (charge introduction) and G674R (charge introduction, opposite sign), the series demonstrates that glycine's role at this position is essential and irreplaceable — any non-glycine substitution produces pathogenic consequence through the same fundamental mechanism. The Atlas's per-variant analysis surfaces this convergence; pre-atlas studies of individual variants would not have seen the pattern.
