MOLECULAR ATLAS · VARIANT CARD

WFS1 G674E — Wolframin

Glycine → Glutamate at position 674 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic, associated with DFNA6 hearing loss. AlphaMissense 0.996 (near-maximum), DynaMut2 ΔΔG -0.34 kcal/mol (destabilising). One of three pathogenic substitutions catalogued at position 674 in the Atlas (with G674R and G674W).

IDENTITY

Variant	G674E (p.Glycine674Glutamate)
DNA change	c.2021G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002203527
Amino acid change	Glycine (G) → Glutamate (E) — the smallest amino acid (backbone-only, maximum flexibility) replaced by a negatively-charged carboxylate-bearing residue. Loss of backbone flexibility plus addition of 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 in a well-folded region (pLDDT 84). Glycine residues in folded domains often serve specific structural roles that other amino acids cannot replicate.
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 local environment is dense — a cysteine and a proline immediately flank G674, suggesting a structurally constrained turn or loop region. The wild-type glycine at 674 plays a backbone-flexibility role. Glycine's lack of a side chain permits backbone conformations that other amino acids cannot adopt — particularly in tight turns and bends. The proximity to CYS673 (which may participate in disulfide chemistry, see C690R/C690Y atlas cards for the C673 contact discussion)

and to PRO675 (a backbone-constraining residue) suggests G674 sits at a deliberately flexible position in a deliberately rigid region. Replacing glycine with glutamate disrupts this on two axes: the backbone flexibility the wild-type provided is gone (glutamate's side chain constrains phi/psi angles), and a negatively-charged carboxylate is introduced into a tight local environment. The ΔΔG of 0.34 indicates the fold absorbs this. AlphaMissense's 0.996 score reflects the severity of the functional consequence. Compare with G674R and G674W at the same position (Atlas cards adjacent): all three substitutions are pathogenic, with different mechanisms (charge introduction for G674E and G674R; volume increase for G674W) but the same root cause — removal of glycine's backbone flexibility from a position that requires it.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.996	**-0.34** kcal/mol	**84.12**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990248765	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2024/06/13 00:00
Inheritance	Autosomal dominant pattern indicated by association with DFNA6 (WFS1-related hearing loss).
WFS1 variant landscape	G674E is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

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. |ΔΔG| = 0.34 kcal/mol — fold survives. AlphaMissense 0.996 (near-maximum) confirms severe functional consequence.

The mechanism is loss of backbone flexibility plus charge introduction into a constrained loop region. Therapeutic strategy: a small molecule that stabilizes the wild-type backbone geometry around the C673-G674-P675 region, or a chaperone biasing the local fold against the variant's preferred geometry.

Compare with G674R (different charge sign) and G674W (volume increase) at the same position — three Atlas variants converge on a single therapeutic target geometry.

Position 674 is one of three positions in this batch where multiple pathogenic substitutions exist (Y669, W700, G674). The G674 series demonstrates glycine's irreplaceable role: no single amino acid can substitute for glycine's backbone flexibility at positions that require it. Drug discovery aimed at the G674 region rescues all three known variants simultaneously.
