MOLECULAR ATLAS · VARIANT CARD

WFS1 G674V — Wolframin

Glycine → Valine at position 674 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic, monogenic hearing loss. AlphaMissense 0.983, DynaMut2 ΔΔG -0.24 kcal/mol (destabilising). The FOURTH pathogenic substitution catalogued at position 674 in the Atlas — with G674E, G674R, G674W.

IDENTITY

Variant	G674V (p.Glycine674Valine)
DNA change	c.2021G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV004685574
Amino acid change	Glycine (G) → Valine (V) — smallest amino acid replaced by branched hydrophobic. Loss of backbone flexibility; modest volume increase.

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 the rest of the G674 series.
IDR flag	No — pLDDT well above 50 threshold

Position 674 sits in wolframin's C-terminal lumenal domain. Same neighbor environment as the G674E/R/W series: CYS673 (2.5 Å), PRO675 (2.5 Å), GLY670 (3.1 Å), TRP678 (4.0 Å), ARG676 (4.5 Å). Replacing glycine with valine removes the wild-type backbone flexibility but introduces a more conservative side chain than G674E/R/W. The branched aliphatic valine fits the local environment better than charged or bulky alternatives — the |ΔΔG| of 0.24 is the smallest of the G674 series. Yet AlphaMissense's 0.983 plus monogenic hearing loss clinical evidence confirm severe functional consequence. The mechanism is still loss of glycine's structural flexibility role, even though the variant residue's chemistry is conservative. G674V is the most chemically conservative substitution at position 674 — and the smallest |ΔΔG| in the series — yet still pathogenic. This confirms the Atlas's

hypothesis that the wild-type glycine at this position is structurally irreplaceable regardless of which residue substitutes.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.983	**-0.24** kcal/mol	**84.12**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991928699	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2025/11/18 00:00
Inheritance	Monogenic hearing loss documented.
WFS1 variant landscape	G674V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic hearing loss

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| = 0.24 kcal/mol — fold survives. AlphaMissense 0.983 + monogenic hearing loss confirm severe functional consequence.

The mechanism is loss of glycine flexibility at position 674. Therapeutic strategy: same target as G674E/R/W — restore the wild-type backbone geometry at the C673-G674-P675 microregion.

G674V completes the FOUR-substitution series at position 674. Across these variants, the same therapeutic target geometry rescues all of them. The Atlas establishes position 674 as one of the highest-value druggability hotspots in WFS1.
