MOLECULAR ATLAS · VARIANT CARD

WFS1 G736R — Wolframin

Glycine → Arginine at position 736 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic. AlphaMissense 0.984, DynaMut2 ΔΔG -0.92 kcal/mol (destabilising). Another glycine-removal variant — paralleling the G674 cluster mechanism.

IDENTITY

Variant	G736R (p.Glycine736Arginine)
DNA change	c.2206G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002734647
Amino acid change	Glycine (G) → Arginine (R) — smallest amino acid replaced by a large, positively-charged guanidinium-bearing residue. Same chemistry shift as G674R but at a different position.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 736	**88.12** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 736 sits in the ER lumen (pLDDT 88).
IDR flag	No — pLDDT well above 50 threshold

Position 736 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places G736 within 5 Å of GLU737 (2.4 Å), TYR735 (2.5 Å), ARG732 (3.1 Å — a four-residue-back contact), HIS766 (3.3 Å — long-range), and ILE767 (4.1 Å). The local environment combines polar (E737, Y735), basic (R732), and titratable (H766) residues with a hydrophobic contact (I767). The wild-type glycine at 736 plays the same backbone-flexibility role described for the G674 cluster. The neighbor analysis shows particularly tight packing — multiple residues within 4 Å — suggesting the local fold is geometrically constrained, and glycine's lack of side chain is what enables that geometry. Notably, ARG732 sits 3.1 Å away; the wild-type G736 plus R732 form a tight cluster where a single basic residue dominates the local electrostatic character. Replacing glycine with arginine adds a second positive charge at 3.1 Å from the existing R732. This produces a two-arginine

cluster similar to the G674R case — local electrostatic repulsion between adjacent positive charges plus the loss of glycine's backbone flexibility. The |ΔΔG| of 0.92 reflects this combined cost. AlphaMissense's 0.984 score captures the severe functional consequence — likely disruption of a specific lumenal interaction surface where R732 alone served as the recognized positive charge.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.984	**-0.92** kcal/mol	**88.12**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990255019	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2022/10/26 00:00
Inheritance	Inheritance not specified. ClinVar Pathogenic classification with multiple submitters.
WFS1 variant landscape	G736R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for G736R — 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| = 0.92 kcal/mol — fold survives. AlphaMissense 0.984 confirms severe functional consequence.

The mechanism is loss of glycine flexibility plus introduction of a second positive charge adjacent to R732 — disrupting a likely partner-recognition surface where R732 alone was the wild-type signature.

Therapeutic strategy: site-directed small molecules at the R732-G736-Y735 microregion. Pharmacological chaperones biasing the local backbone toward the wild-type glycine-enabled geometry.

G736R parallels the G674R mechanism — glycine removal in a tightly-packed loop adjacent to an existing arginine. The Atlas's per-variant analysis shows that this 'glycine-adjacent-to-arginine' pattern repeats multiple times across the WFS1 lumenal domain, and substitutions at the glycine positions are consistently pathogenic. The class is a coherent therapeutic target — drug discovery against the geometric niche of these glycines.
