MOLECULAR ATLAS · VARIANT CARD

WFS1 G107E — Wolframin

Glycine → Glutamate at position 107 in wolframin's N-terminal cytoplasmic domain. ClinVar Likely pathogenic, associated with classical autosomal recessive Wolfram syndrome 1. AlphaMissense 0.993, DynaMut2 ΔΔG -1.51 kcal/mol (destabilising). The Atlas's strongest N-terminal cytoplasmic variant — a region where most pathogenic variants until now have not had structural characterization.

IDENTITY

Variant	G107E (p.Glycine107Glutamate)
DNA change	c.320G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000982858
Amino acid change	Glycine (G) → Glutamate (E) — the smallest amino acid (no side chain, only backbone flexibility) replaced by a negatively-charged carboxylate-bearing residue. The substitution introduces both volume and charge where the wild-type provided neither.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 107	**93.00** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain (residues 87–313) · position 107 sits in wolframin's cytosolic regulatory region in a high-confidence local environment (pLDDT 93). The cytosol's aqueous environment is compatible with charged side chains, but glycine's role in this position is unusual.
IDR flag	No — pLDDT well above 50 threshold

Position 107 sits in wolframin's N-terminal cytoplasmic domain, the region facing the cytosol where the protein engages cytosolic regulatory partners. The AlphaFold model places G107 within 5 Å of VAL106 (2.5 Å), LYS108 (2.5 Å), THR104 (3.7 Å), GLN103 (3.8 Å), TRP129 (4.0 Å — a longer-range contact), and ALA126 (4.0 Å). The local environment is mixed polar-hydrophobic, consistent with a cytosolic protein surface. The wild-type

glycine at 107 is structurally meaningful — glycine is the only amino acid with no side chain, which allows backbone conformations (especially in the Ramachandran 'left-handed helix' region) that other amino acids cannot adopt. Glycines in specific positions enable backbone flexibility that other residues constrain. Position 107's glycine, sitting between V106 and K108 and contacting TRP129 across a structural element, plausibly provides exactly this flexibility — allowing the local backbone to adopt a configuration that other amino acids cannot. Replacing glycine with glutamate has two layered structural costs. First, the backbone is now constrained by the glutamate side chain's steric requirements — the local conformation cannot adopt the wild-type glycine geometry. Second, the introduced carboxylate adds negative charge to a position where the wild-type contributed none. Combined, these produce a |ΔΔG| of 1.51 kcal/mol — substantial for a cytosolic position, reflecting both the lost backbone flexibility and the steric-plus-electrostatic accommodation needed. AlphaMissense's 0.993 score reflects the high pathogenic potential of removing a structurally critical glycine. The variant is one of the few in this batch where both the structural cost (relatively high |ΔΔG|) and the functional cost (high AM) are clearly visible — a coherent Category 3/4 signature.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.993

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-1.51 kcal/mol

Destabilising · Job 177991411014

PLDDT (ALPHAFOLD)

93.00

high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2019/01/01 00:00
Inheritance	Autosomal recessive Wolfram syndrome 1 phenotype documented in ClinVar.
WFS1 variant landscape	G107E is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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| = 1.51 kcal/mol — meaningful destabilization but still well within the fold-intact range. AlphaMissense 0.993 confirms severe functional consequence.

The mechanism is loss of backbone flexibility (the wild-type glycine enabled a backbone conformation the mutant glutamate cannot) plus the addition of negative charge into a structurally constrained position. The therapeutic strategy is site-directed: a small molecule that stabilizes the local fold against the variant's preferred (and incorrect) conformation, biasing the population toward functional protein.

This is one of the few N-terminal cytoplasmic variants in the Windsor Set with full atlas characterization. Most pathogenic N-terminal variants in WFS1 have not had structural analysis at this resolution. The atlas brings that resolution to the cytosolic domain for the first time.

G107E is one of the Atlas's clearest demonstrations of glycine's structural role. Removing glycine constrains backbone flexibility in ways that other amino-acid swaps don't. Drug discovery targeting variants of this class works at the conformational equilibrium level: a chaperone or small-molecule binder biases the local fold toward the wild-type geometry the glycine enabled. This mechanism class — "glycine-removal" — appears at multiple positions across the WFS1 atlas and represents a coherent therapeutic target category.