MOLECULAR ATLAS · VARIANT CARD

WFS1 A31G — Wolframin

Alanine → Glycine at position 31 in wolframin's N-terminal intrinsically disordered region (IDR). ClinVar carries conflicting classifications. AlphaMissense 0.100 (likely BENIGN). pLDDT 28 — deep IDR. DynaMut2 ΔΔG -0.35 kcal/mol but NOT trustworthy. A Category 5 IDR variant flagged for wet-lab validation.

IDENTITY

Variant	A31G (p.Alanine31Glycine)
DNA change	c.92C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215373
Amino acid change	Alanine (A) → Glycine (G) — a small hydrophobic methyl-bearing residue replaced by the smallest amino acid (no side chain). The substitution removes a methyl group and adds backbone flexibility.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 31	**28.33** BELOW IDR THRESHOLD
Domain	N-terminal intrinsically disordered region (1-86)
Position context	N-terminal intrinsically disordered region (residues 1–86) · position 31 sits in a region with pLDDT 28, deep in IDR territory. The AlphaFold model is not predictive here.
IDR flag	YES — pLDDT 28.33 is below 50 threshold (route to Cat 5)

Position 31 sits in wolframin's N-terminal IDR. The pLDDT score of 28 indicates that AlphaFold cannot reliably predict the local conformation — the protein adopts an ensemble of structures in this region rather than a single fold. Neighbor analysis returns only the immediate sequence neighbors (SER32 at 2.5 Å, THR30 at 2.6 Å, LEU33 at 4.6 Å) — the structural signature of IDR. Replacing alanine with glycine adds backbone flexibility. Glycine permits backbone conformations (especially in the Ramachandran left-handed helix region) that other amino acids cannot adopt. In a folded protein this is sometimes structurally significant. In an IDR, where the protein is

already conformationally heterogeneous, the impact is more subtle — the ensemble's accessible conformational space shifts slightly, but no single 'wild-type' geometry is being broken. DynaMut2's |ΔΔG| of 0.35 kcal/mol is not interpretable as a quantitative claim in this region. AlphaMissense's 0.100 score (well below the 0.564 pathogenic threshold) considers the variant likely benign. The conflicting ClinVar classifications — some pathogenic, some uncertain — likely reflect that this variant has been observed in patients with Wolfram-spectrum disease but causal contribution has not been firmly established. The mechanism, if pathogenic, would likely involve IDR-mediated phase separation, partner binding through disordered regions, or context-dependent functional disruption — none of which AlphaMissense's training reliably captures.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.100

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.35 kcal/mol

Destabilising · Job 177992520829

PLDDT (ALPHAFOLD)

28.33

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/09/10 00:00
Inheritance	Inheritance pattern uncertain given conflicting ClinVar classifications. Documented in patients with Wolfram syndrome and inborn genetic diseases.
WFS1 variant landscape	A31G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Inborn genetic diseases
- 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 5 — IDR Exclusion. pLDDT = 28 places this variant deep in wolframin's IDR. DynaMut2 stability predictions are not trustworthy here. AlphaMissense's score of 0.100 (likely benign) raises a substantive question about whether the variant is genuinely pathogenic or is a benign variant observed by association.

The Atlas routes Category 5 variants to wet-lab characterization rather than computational drug discovery. For A31G specifically, the recommended next steps are: (1) verify the clinical association with case-by-case review; (2) characterize the IDR's functional role; (3) test the variant in functional assays. Therapeutic strategy decisions should not be made on the current computational data alone.

A31G is one of two IDR-pair Category 5 variants in this batch (with G78R). Both sit in wolframin's N-terminal disordered region, both have AlphaMissense scores in the likely-benign range, both carry conflicting ClinVar classifications. The Atlas appropriately flags these as exclusions from the computational drug discovery pipeline. Pre-atlas analysis might have included them as therapeutic targets; the Atlas's IDR-exclusion logic is what prevents that misallocation of effort.