MOLECULAR ATLAS · VARIANT CARD

WFS1 G78R — Wolframin

Glycine → Arginine at position 78 in wolframin's N-terminal intrinsically disordered region (IDR). ClinVar carries conflicting classifications. AlphaMissense 0.106 (likely BENIGN by AM, not pathogenic). pLDDT 26 — deep IDR. DynaMut2 ΔΔG -0.48 kcal/mol but NOT trustworthy in this region. A Category 5 IDR variant that requires wet-lab characterization.

IDENTITY

Variant	G78R (p.Glycine78Arginine)
DNA change	c.232G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000903896
Amino acid change	Glycine (G) → Arginine (R) — the smallest amino acid (backbone-only) replaced by a large, positively-charged guanidinium-bearing residue. Major chemistry shift, but the structural consequence depends on the local fold — and in an IDR, there is no well-defined local fold to disrupt.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 78	**26.22** BELOW IDR THRESHOLD
Domain	N-terminal intrinsically disordered region (1-86)
Position context	N-terminal intrinsically disordered region (residues 1–86) · position 78 sits in a region with pLDDT 26, deep in IDR territory. The AlphaFold model is not predictive in this region; the protein adopts an ensemble of conformations rather than a single fold.
IDR flag	YES — pLDDT 26.22 is below 50 threshold (route to Cat 5)

Position 78 sits in wolframin's N-terminal intrinsically disordered region (IDR), spanning residues 1–86. The pLDDT score of 26 indicates that AlphaFold's predicted geometry at this position is essentially unreliable — the structure shown in the model does not represent a single dominant conformation but rather an arbitrary picked sample from an ensemble. The AlphaFold-derived neighbor analysis shows only PRO79 (2.5 Å) and THR77 (2.5 Å) — the

immediate sequence neighbors and nothing else within 5 Å. This is itself a structural signature of IDR: in folded domains, every residue has multiple cross-chain neighbors at structural contact distance. In IDRs, only sequence neighbors appear because the chain has no consistent tertiary structure. The DynaMut2 |ΔΔG| of 0.48 kcal/mol is therefore not trustworthy as a quantitative claim about the variant's structural impact. DynaMut2 assumes a meaningful input fold; IDR positions violate that assumption. What is more revealing is the AlphaMissense score of 0.106 — well below the 0.564 likely-pathogenic threshold. AlphaMissense considers this variant likely benign. And yet ClinVar carries conflicting classifications including documented Wolfram-related conditions. The disconnect suggests either: (a) the variant is genuinely benign and clinical reports represent false-positive pathogenic calls or population-stratification artifacts; (b) the variant is pathogenic by a mechanism (e.g., IDR-mediated phase separation, partner binding through disordered region) that AlphaMissense's training does not capture; or (c) the variant's pathogenicity depends on context (e.g., compound heterozygosity with another WFS1 variant) that single-variant analysis cannot resolve. None of these can be settled from the structural data alone.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.106

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.48 kcal/mol

Destabilising · Job 177992511391

PLDDT (ALPHAFOLD)

26.22

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/05/19 00:00
Inheritance	Documented in association with DFNA6 (AD WFS1-related hearing loss) and Wolfram-like syndrome. Inheritance pattern uncertain given conflicting ClinVar classifications.
WFS1 variant landscape	G78R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

- Wolfram-like syndrome

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 = 26 places this variant deep in the intrinsically disordered region of wolframin. DynaMut2 stability predictions are not trustworthy in this region. AlphaMissense's score of 0.106 (likely benign) further questions the variant's pathogenic mechanism.

The Atlas explicitly routes Category 5 variants away from computational drug discovery and toward wet-lab characterization. Recommended next steps: (1) confirm clinical penetrance with additional case data; (2) characterize the IDR's role in wolframin partner interactions experimentally; (3) test the variant in cell-based functional assays before drawing therapeutic conclusions.

Until experimental data clarifies the mechanism, this variant should NOT drive therapeutic strategy.

G78R demonstrates the value of the Atlas's Category 5 IDR exclusion. The conflicting clinical classifications + low AlphaMissense score + deep IDR location together flag the variant as one where the standard computational pipeline cannot reliably characterize pathogenicity. Pre-atlas drug discovery might have treated this position the same as any other Wolfram-spectrum variant. The Atlas surfaces the appropriate caution — Cat 5, wet-lab first, no computational drug design until the mechanism is clarified.
