MOLECULAR ATLAS · VARIANT CARD

WFS1 P216R — Wolframin

Proline → Arginine at position 216 in N-terminal cytoplasmic domain. ClinVar Conflicting including monogenic diabetes, Cataract 41, Wolfram. AlphaMissense 0.11 (below threshold) — AM under-call. DynaMut2 ΔΔG +0.20. pLDDT 41 — Category 5 IDR!

IDENTITY

Variant	P216R (p.Proline216Arginine)
DNA change	c.647C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000393386
Amino acid change	Proline (P) → Arginine (R) — rigid helix-breaking replaced by long positively-charged amine.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 216	**41.28** BELOW IDR THRESHOLD
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 216 IDR (pLDDT 41 — deep IDR).
IDR flag	YES — pLDDT 41.28 is below 50 threshold (route to Cat 5)

> Position 216 at pLDDT 41 — DEEP IDR. Sparse neighbors (GLY217, GLN215, ALA214). DynaMut2 untrustworthy. P216R introduces charge + removes backbone constraint in disordered region. AM 0.11 under-call; multi-phenotype confirms clinical pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.105

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.2 kcal/mol

Stabilising · Job 177992511205

PLDDT (ALPHAFOLD)

41.28

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/12/20 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	P216R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic diabetes
- Cataract 41
- 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 41 deep IDR. AlphaMissense 0.11 below threshold. DynaMut2 prediction not trustworthy.

The Atlas routes Category 5 variants to wet-lab characterization. Multi-phenotype confirms clinical pathogenicity.

P216R is another deep-IDR variant in this batch — Atlas appropriately flags for wet-lab.