MOLECULAR ATLAS · VARIANT CARD

WFS1 R42Q — Wolframin

Arg→Gln p42 IDR AM=0.07 ddg=-0.05 pLDDT=29. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	R42Q (p.Arginine42Glutamine)
DNA change	c.125G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000517412
Amino acid change	charge loss, amide preserved

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 42	**28.84** BELOW IDR THRESHOLD
Domain	N-terminal intrinsically disordered region (1-86)
Position context	N-terminal IDR
IDR flag	YES — pLDDT 28.84 is below 50 threshold (route to Cat 5)

> Position analysis: ALA43 (2.4 Å — A43V!), PRO41 (2.5 Å), ARG40 (4.8 Å). pLDDT 29 deep IDR. Adjacent to A43V. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.069

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.05 kcal/mol

Destabilising · Job 177992526394

PLDDT (ALPHAFOLD)

28.84

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/06/12 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	R42Q is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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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Cat 5 IDR — see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally identified. Therapeutic strategy: site-directed at contacts identified above, or wet-lab validation if pLDDT borderline/below 50.

IDR adjacent to A43V.
