MOLECULAR ATLAS · VARIANT CARD

WFS1 A43V — Wolframin

Ala→Val p43 IDR AM=0.08 ddg=-1.11 pLDDT=28. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	A43V (p.Alanine43Valine)
DNA change	c.128C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000166568
Amino acid change	conservative volume increase

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 43	**28.23** BELOW IDR THRESHOLD
Domain	N-terminal intrinsically disordered region (1-86)
Position context	N-terminal IDR
IDR flag	YES — pLDDT 28.23 is below 50 threshold (route to Cat 5)

Position analysis: ARG42 (2.5 Å — R42Q!), PRO44 (2.5 Å), PRO41 (4.9 Å). pLDDT 28 deep IDR. Substantial ΔΔG but untrustworthy. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.077

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-1.11 kcal/mol

Destabilising · Job 177992522666

PLDDT (ALPHAFOLD)

28.23

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2013/11/06 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	A43V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

RESEARCH PATH DECISION TREE

```
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
```

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.

Deep IDR adjacent to R42Q.
