MOLECULAR ATLAS · VARIANT CARD

WFS1 A58V — Wolframin

Ala→Val p58 IDR AM=0.09 ddg=-0.68 pLDDT=26. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	A58V (p.Alanine58Valine)
DNA change	c.173C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000516852
Amino acid change	conservative volume increase

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 58	**26.17** BELOW IDR THRESHOLD
Domain	N-terminal intrinsically disordered region (1-86)
Position context	N-terminal IDR
IDR flag	YES — pLDDT 26.17 is below 50 threshold (route to Cat 5)

Position analysis: ALA59 (2.5 Å), ALA57 (2.5 Å — partner of A57S/A57T). pLDDT 26 deep IDR. Multiple A57 substitutions Atlas-tracked. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.087

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.68 kcal/mol

Destabilising · Job 177992518683

PLDDT (ALPHAFOLD)

26.17

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/07 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	A58V 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.

Deep IDR — multi-substitution position cluster 57-58.
