MOLECULAR ATLAS · VARIANT CARD

WFS1 A57T — Wolframin

Ala→Thr p57 IDR AM=0.07 ddg=+0.07 pLDDT=27. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	A57T (p.Alanine57Threonine)
DNA change	c.169G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000252656
Amino acid change	polarity into IDR

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 57	**27.34** BELOW IDR THRESHOLD
Domain	N-terminal intrinsically disordered region (1-86)
Position context	N-terminal IDR
IDR flag	YES — pLDDT 27.34 is below 50 threshold (route to Cat 5)

Position analysis: ALA58 (2.4 Å), ASP56 (2.5 Å). pLDDT 27 deep IDR. THIRD substitution at position 57 (A57S, A57T). The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.068

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.07 kcal/mol

Stabilising · Job 177992523818

PLDDT (ALPHAFOLD)

27.34

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/12/10 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	A57T 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.

Position 57 IDR three-substitution cluster.
