

WFS1 A57S — Wolframin

Ala→Ser p57 IDR AM=0.08 ddg=+0.1 pLDDT=27. ClinVar Conflicting evidence.
Atlas mechanism: see structural analysis.

IDENTITY

Variant	A57S (p.Alanine57Serine)
DNA change	c.169G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215374
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 — A58V/T), ASP56 (2.5 Å). pLDDT 27 deep IDR. Multi-substitution at 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

0.081am_class: **LBen** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **0.1** kcal/molStabilising · Job
177992519633

PLDDT (ALPHAFOLD)

27.34

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	CONFLICTING CLASSIFICATIONS OF PATHOGENICITY
Review status	criteria provided, conflicting classifications
Last evaluated	2025/06/19 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	A57S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

RESEARCH PATH DECISION TREE

$\Delta\Delta G < 2$ + binding site affected → CATEGORY 3 – docking experiments $\Delta\Delta G$ 2–4 → CATEGORY 2 – pharmacological chaperones $\Delta\Delta G > 4$ → 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.

Position 57 multi-substitution IDR cluster.