

WFS1 A58T — Wolframin

Ala→Thr p58 IDR AM=0.08 ddg=+0.05 pLDDT=26. ClinVar Conflicting evidence.
Atlas mechanism: see structural analysis.

IDENTITY

| | |
|-------------------|-----------------------------|
| Variant | A58T (p.Alanine58Threonine) |
| DNA change | c.172G>A |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV000393384 |
| Amino acid change | polarity into IDR |

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). pLDDT 26 deep IDR. Third substitution near 57-58 cluster. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.077am_class: **LBen** —
threshold > 0.564

DYNAMUT2 ΔΔG

0.05 kcal/molStabilising · Job
177992519804

PLDDT (ALPHAFOLD)

26.17

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

| | |
|------------------------|--|
| ClinVar classification | CONFLICTING CLASSIFICATIONS OF PATHOGENICITY |
| Review status | criteria provided, conflicting classifications |
| Last evaluated | 2021/11/02 00:00 |
| Inheritance | Conflicting ClinVar classifications. |
| WFS1 variant landscape | A58T 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 57-58 IDR multi-substitution.