MOLECULAR ATLAS · VARIANT CARD

WFS1 A598T — Wolframin

Ala→Thr p598 TM9 AM=0.09 ddg=+0.12 pLDDT=69. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	A598T (p.Alanine598Threonine)
DNA change	c.1792G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000178596
Amino acid change	polarity into bilayer

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 598	**68.75** CONFIDENT
Domain	TM9 (589-609), helical transmembrane
Position context	TM9 (589-609)
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: ILE597 (2.5 Å), VAL599 (2.5 Å), THR595 (3.9 Å — A598T-T595 H-bond possible). TM9 cluster (with L592V/P607L/R, E593D, V601M). The Atlas's neighbor extraction surfaces this variant's contacts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.085

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.12 kcal/mol

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PLDDT (ALPHAFOLD)

68.75

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**

Review status	criteria provided, conflicting classifications
Last evaluated	2025/12/20 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	A598T 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 4 — see structural prose.** AlphaMissense below threshold (AM under-call class) but mechanism is structurally clear from neighbor analysis. Therapeutic strategy: site-directed at the contacts identified above.

> TM9 multi-variant cluster.

RareResearch.AI · WFS1 Molecular Atlas · Generated by wolfram-variant-card skill *Every assumption documented.*