MOLECULAR ATLAS · VARIANT CARD

WFS1 T590M — Wolframin

Thr→Met p590 TM9 AM=0.06 ddg=+0.09 pLDDT=73. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	T590M (p.Threonine590Methionine)
DNA change	c.1769C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000505398
Amino acid change	polar→hydrophobic

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 590	**72.56** **HIGH CONFIDENCE**
Domain	TM9 (589-609), helical transmembrane
Position context	TM9 (589-609)
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: SER591 (2.5 Å), PHE589 (2.5 Å — TM9 start), ARG587 (3.8 Å — R587W/Q!). TM9 cluster + loop boundary. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.062

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.09 kcal/mol

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PLDDT (ALPHAFOLD)

72.56

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2023/04/17 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	T590M 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 identified. Therapeutic strategy: site-directed at contacts identified above, or wet-lab validation if pLDDT borderline/below 50.

TM9 cluster + R587 loop boundary.

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