MOLECULAR ATLAS · VARIANT CARD

WFS1 A684T — Wolframin

Alanine → Threonine at position 684 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic. AlphaMissense 0.952, DynaMut2 ΔΔG +0.11 kcal/mol — essentially neutral (slightly stabilising). A polar-introduction variant adjacent to the R685 position (R685P atlas card).

IDENTITY

Variant	A684T (p.Alanine684Threonine)
DNA change	c.2050G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001458816
Amino acid change	Alanine (A) → Threonine (T) — a small hydrophobic methyl-bearing residue replaced by a small polar hydroxyl-bearing residue. The substitution adds H-bond donor/acceptor capacity at a position that previously had none.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 684	**87.94** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 684 in the ER lumen (pLDDT 88). Immediately adjacent to R685 in sequence.
IDR flag	No — pLDDT well above 50 threshold

Position 684 sits in wolframin's C-terminal lumenal domain, immediately preceding R685. The AlphaFold model places A684 within 5 Å of MET683 (2.5 Å), ARG685 (2.5 Å — the partner residue in R685P atlas card), GLN687 (4.0 Å), ASN682 (4.0 Å), and THR686 (4.4 Å). The local environment is heavy on polar and basic residues (R685, Q687, N682, T686). The wild-type alanine at 684 provides minimal side-chain volume and no functional groups — it serves as a steric placeholder between M683 and R685. Replacing it with threonine introduces a polar hydroxyl group into a polar-rich environment. The hydroxyl could either form a new hydrogen bond with R685, T686, N682, or Q687, or perturb the existing H-bond network among those residues. The ΔΔG of +0.11 indicates near-neutral structural impact — the new H-bonding option roughly compensates for any local strain. But AlphaMissense's 0.952

score plus the ClinVar Pathogenic classification confirm pathogenic mechanism. The mechanism is most plausibly disruption of the R685 H-bond network. The wild-type A684 placeholder allows R685 to project its side chain in a specific direction; the introduced T684 hydroxyl competes for R685's H-bonding attention and pulls it out of its functional orientation. Combined with the R685P atlas card (same R685 environment disrupted from the other side), this microregion has two convergent therapeutic targets.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.952	**0.11** kcal/mol	**87.94**
am_class: **LPath** — threshold > 0.564	Stabilising · Job 177990264347	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/10/15 00:00
Inheritance	Inheritance not specified. ClinVar Pathogenic.
WFS1 variant landscape	A684T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for A684T — ClinVar Pathogenic by review evidence)

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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Category 4 — Stable Fold, Function Disrupted. ΔΔG = +0.11 kcal/mol — essentially no fold change. AlphaMissense 0.952 confirms pathogenic functional consequence.

The mechanism is introduction of a new H-bond donor that captures or redirects R685's functional H-bonding, disrupting the partner-recognition surface R685 normally provides. Drug discovery targets the R685 microregion — same target as R685P, approached from a different angle.

Two Atlas variants in the same 683-687 region converge on a single therapeutic geometry: a small molecule that stabilizes the wild-type R685 orientation.

A684T pairs with R685P in the Atlas as sister variants at adjacent positions, both disrupting the same R685 partner-recognition geometry. The two are pedagogically important: they show that pathogenic variants don't have to be at the same position to share a therapeutic target — adjacent positions with overlapping structural roles produce the same drug-discovery opportunity.
