

WFS1 A393T — Wolframin

Alanine → Threonine at position 393. Cytoplasmic loop 2. ClinVar Uncertain significance, AlphaMissense 0.710, DynaMut2 $\Delta\Delta G$ -1.89 kcal/mol (destabilising).

IDENTITY

Variant	A393T (p.Alanine393Threonine)
DNA change	c.1177G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001979339
Amino acid change	Alanine (A) → Threonine (T)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 393	79.88 HIGH CONFIDENCE
Domain	Cytoplasmic loop 2
Position context	Loop region · position 393 sits between transmembrane segments, solvent-accessible
IDR flag	No — pLDDT well above 50 threshold

Position 393 sits in a connecting loop between transmembrane helices. Loop residues are typically solvent-exposed and often contribute to interhelical contacts or serve as recognition sites for binding partners. The wild-type residue is small/hydrophobic (alanine — methyl sidechain); the mutant is small polar (threonine — hydroxyl). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.710

am_class: **likely pathogenic** —
threshold > 0.564

DYNAMUT2 $\Delta\Delta G$ **-1.89** kcal/mol

Destabilising · Job
178092125261

PLDDT (ALPHAFOLD)

79.88

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2022/04/26 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	A393T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) <ul style="list-style-type: none">(no 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

Category 3/4 — Most Druggable

$|\Delta\Delta G|=1.89 < 2$ kcal/mol (fold intact) + AlphaMissense 0.710 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframín's fold survives this substitution ($|\Delta\Delta G|=1.89$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.710. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.