

# WFS1 A458T — Wolframin

Alanine → Threonine at position 458. Cytoplasmic loop 3. ClinVar Uncertain significance, AlphaMissense 0.674, DynaMut2  $\Delta\Delta G$  -1.81 kcal/mol (destabilising).

## IDENTITY

Variant	A458T (p.Alanine458Threonine)
DNA change	c.1372G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002149077
Amino acid change	Alanine (A) → Threonine (T)

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 458	<b>86.69</b> HIGH CONFIDENCE
Domain	Cytoplasmic loop 3
Position context	Loop region · position 458 sits between transmembrane segments, solvent-accessible
IDR flag	No — pLDDT well above 50 threshold

Position 458 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

**0.674**

am\_class: **likely pathogenic** —  
threshold > 0.564

DYNAMUT2  $\Delta\Delta G$ **-1.81** kcal/mol

Destabilising · Job  
178092127084

PLDDT (ALPHAFOLD)

**86.69**

high confidence

## CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2024/10/15 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	A458T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) <ul style="list-style-type: none"><li>• Autosomal dominant nonsyndromic hearing loss 6</li><li>• Type 2 diabetes mellitus</li><li>• Wolfram-like syndrome</li><li>• Cataract 41</li><li>• Wolfram syndrome 1</li></ul>

## 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

$|\Delta\Delta G|=1.81 < 2$  kcal/mol (fold intact) + AlphaMissense 0.674 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution ( $|\Delta\Delta G|=1.81$  kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.674. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.