

# WFS1 S502I — Wolframin

Serine → Isoleucine at position 502. Transmembrane helix 7. ClinVar Uncertain significance, AlphaMissense 0.980, DynaMut2  $\Delta\Delta G$  -0.05 kcal/mol (destabilising).

## IDENTITY

Variant	S502I (p.Serine502Isoleucine)
DNA change	c.1505G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV004279899
Amino acid change	Serine (S) → Isoleucine (I)

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 502	<b>79.38</b> HIGH CONFIDENCE
Domain	Transmembrane helix 7
Position context	Inside Transmembrane helix 7 · position 502 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 502 sits in a transmembrane helix (Transmembrane helix 7). Wolframin has eleven such helices anchoring it in the ER membrane; substitutions inside the bilayer-embedded segments can disrupt helix packing, lipid contacts, and the overall ER topology of the protein. The wild-type residue is small polar (serine — hydroxyl); the mutant is medium hydrophobic (isoleucine — branched). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.980**am\_class: **likely pathogenic** —  
threshold > 0.564DYNAMUT2  $\Delta\Delta G$ **-0.05** kcal/molDestabilising · Job  
178092094306

PLDDT (ALPHAFOLD)

**79.38**

high confidence

## CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2025/08/18 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	S502I 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>• Wolfram-like syndrome</li><li>• Type 2 diabetes mellitus</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

$|\Delta\Delta G|=0.05 < 2$  kcal/mol (fold intact) + AlphaMissense 0.980 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframins fold survives this substitution ( $|\Delta\Delta G|=0.05$  kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.980. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.