

# WFS1 S446N — Wolframin

Serine → Asparagine at position 446. Transmembrane helix 5. ClinVar Uncertain significance, AlphaMissense 0.773, DynaMut2  $\Delta\Delta G$  +0.17 kcal/mol (stabilising).

## IDENTITY

Variant	S446N (p.Serine446Asparagine)
DNA change	c.1337G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003981552
Amino acid change	Serine (S) → Asparagine (N)

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 446	<b>82.25</b> HIGH CONFIDENCE
Domain	Transmembrane helix 5
Position context	Inside Transmembrane helix 5 · position 446 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 446 sits in a transmembrane helix (Transmembrane helix 5). 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 polar amide (asparagine — H-bond donor/acceptor). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.773**

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

DYNAMUT2  $\Delta\Delta G$ **0.17** kcal/mol

Stabilising · Job 178092118847

PLDDT (ALPHAFOLD)

**82.25**

high confidence

## CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/06/07 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	S446N is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)
	<ul style="list-style-type: none"><li>Inborn genetic diseases</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

$|\Delta\Delta G|=0.17 < 2$  kcal/mol (fold intact) + AlphaMissense 0.773 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframín's fold survives this substitution ( $|\Delta\Delta G|=0.17$  kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.773. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.