

WFS1 I777S — Wolframin

Isoleucine → Serine at position 777. C-terminal ER-luminal (calcium binding. ClinVar Uncertain significance, AlphaMissense 0.984, DynaMut2 $\Delta\Delta G$ -2.99 kcal/mol (destabilising).

IDENTITY

Variant	I777S (p.Isoleucine777Serine)
DNA change	c.2330T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001317056
Amino acid change	Isoleucine (I) → Serine (S)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 777	92.31 HIGH CONFIDENCE
Domain	C-terminal ER-luminal (calcium binding, calmodulin, chaperone)
Position context	C-terminal luminal domain · position 777 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

Position 777 sits in the C-terminal luminal domain (residues 653–869), wolframin's largest soluble region. This domain projects into the ER lumen and is implicated in calcium handling, ER stress sensing, and protein–protein interactions with ATF6 and Na⁺/K⁺ ATPase β 1. The wild-type residue is medium hydrophobic (isoleucine — branched); the mutant is small polar (serine — hydroxyl). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.984am_class: **likely pathogenic** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-2.99** kcal/molDestabilising · Job
178092091864

PLDDT (ALPHAFOLD)

92.31

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2023/01/05 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	I777S 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 2 — Moderately Destabilizing

$|\Delta\Delta G|=2.99$ in the 2–4 range. Pharmacological chaperone candidate.