

WFS1 W371S — Wolframin

Tryptophan → Serine at position 371. Transmembrane helix 3. ClinVar Uncertain significance, AlphaMissense 0.947, DynaMut2 $\Delta\Delta G$ -2.54 kcal/mol (destabilising).

IDENTITY

Variant	W371S (p.Tryptophan371Serine)
DNA change	c.1112G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003692844
Amino acid change	Tryptophan (W) → Serine (S)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 371	80.25 HIGH CONFIDENCE
Domain	Transmembrane helix 3
Position context	Inside Transmembrane helix 3 · position 371 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 371 sits in a transmembrane helix (Transmembrane helix 3). 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 bulky aromatic (tryptophan — indole ring); 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

0.947am_class: **likely pathogenic** — threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-2.54** kcal/mol

Destabilising · Job 178092140675

PLDDT (ALPHAFOLD)

80.25

high confidence

CLINICAL EVIDENCE

ClinVar classification

UNCERTAIN SIGNIFICANCE

Review status

criteria provided, single submitter

Last evaluated

2024/04/15 00:00

Inheritance

Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.

WFS1 variant landscape

W371S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (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

$|\Delta\Delta G|=2.54$ in the 2–4 range. Pharmacological chaperone candidate.