

WFS1 W371G — Wolframin

Tryptophan → Glycine at position 371. Transmembrane helix 3. ClinVar Uncertain significance, AlphaMissense 0.908, DynaMut2 $\Delta\Delta G$ -2.34 kcal/mol (destabilising).

IDENTITY

Variant	W371G (p.Tryptophan371Glycine)
DNA change	c.1111T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001520543
Amino acid change	Tryptophan (W) → Glycine (G)

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/flexible (glycine — backbone flexibility, no sidechain). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.908am_class: **likely pathogenic** — threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-2.34** kcal/mol

Destabilising · Job 178092106001

PLDDT (ALPHAFOLD)

80.25

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2021/09/20 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	W371G 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

$|\Delta\Delta G|=2.34$ in the 2–4 range. Pharmacological chaperone candidate.