

# WFS1 G581D — Wolframin

Glycine → Aspartic acid at position 581. Transmembrane helix 9. ClinVar Uncertain significance, AlphaMissense 0.743, DynaMut2  $\Delta\Delta G$  -0.53 kcal/mol (destabilising).

## IDENTITY

Variant	G581D (p.Glycine581Aspartic acid)
DNA change	c.1742G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003687973
Amino acid change	Glycine (G) → Aspartic acid (D)

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 581	<b>85.50</b> HIGH CONFIDENCE
Domain	Transmembrane helix 9
Position context	Inside Transmembrane helix 9 · position 581 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 581 sits in a transmembrane helix (Transmembrane helix 9). 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/flexible (glycine — backbone flexibility, no sidechain); the mutant is negatively charged (aspartate — carboxylate). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.743**

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

DYNAMUT2  $\Delta\Delta G$ **-0.53** kcal/mol

Destabilising · Job  
178092121533

PLDDT (ALPHAFOLD)

**85.50**

high confidence

## CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2024/04/25 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	G581D is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) <ul style="list-style-type: none"><li>(no conditions catalogued)</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

$|\Delta\Delta G|=0.53 < 2$  kcal/mol (fold intact) + AlphaMissense 0.743 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframín's fold survives this substitution ( $|\Delta\Delta G|=0.53$  kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.743. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.