

# WFS1 W678G — Wolframin

Tryptophan → Glycine at position 678. C-terminal ER-luminal (calcium binding. ClinVar Uncertain significance/Uncertain risk allele, AlphaMissense 0.964, DynaMut2  $\Delta\Delta G$  -3.13 kcal/mol (destabilising).

## IDENTITY

Variant	W678G (p.Tryptophan678Glycine)
DNA change	c.2032T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000666956
Amino acid change	Tryptophan (W) → Glycine (G)

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 678	<b>82.62</b> HIGH CONFIDENCE
Domain	C-terminal ER-luminal (calcium binding, calmodulin, chaperone)
Position context	C-terminal luminal domain · position 678 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

Position 678 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<sup>+</sup>/K<sup>+</sup> ATPase  $\beta$ 1. 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

**0.964**am\_class: **likely pathogenic** —  
threshold > 0.564DYNAMUT2  $\Delta\Delta G$ **-3.13** kcal/molDestabilising · Job  
178092098041

PLDDT (ALPHAFOLD)

**82.62**

high confidence

## CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE/UNCERTAIN RISK ALLELE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2019/02/11 00:00
Inheritance	Autosomal recessive Wolfram syndrome 1 phenotype documented.
WFS1 variant landscape	W678G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

## 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

$|\Delta\Delta G|=3.13$  in the 2–4 range. Pharmacological chaperone candidate.