

# WFS1 G398R — Wolframin

Glycine → Arginine at position 398. Cytoplasmic loop 2. ClinVar Uncertain significance, AlphaMissense 0.889, DynaMut2  $\Delta\Delta G$  -0.22 kcal/mol (destabilising).

## IDENTITY

Variant	G398R (p.Glycine398Arginine)
DNA change	c.1192G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215411
Amino acid change	Glycine (G) → Arginine (R)

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 398	<b>78.38</b> HIGH CONFIDENCE
Domain	Cytoplasmic loop 2
Position context	Loop region · position 398 sits between transmembrane segments, solvent-accessible
IDR flag	No — pLDDT well above 50 threshold

Position 398 sits in a connecting loop between transmembrane helices. Loop residues are typically solvent-exposed and often contribute to interhelical contacts or serve as recognition sites for binding partners. The wild-type residue is small/flexible (glycine — backbone flexibility, no sidechain); the mutant is positively charged (arginine — guanidinium, strong H-bond donor). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.889**am\_class: **likely pathogenic** — threshold > 0.564DYNAMUT2  $\Delta\Delta G$ **-0.22** kcal/mol

Destabilising · Job 178092108498

PLDDT (ALPHAFOLD)

**78.38**

high confidence

## CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2014/09/18 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	G398R 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

$|\Delta\Delta G|=0.22 < 2$  kcal/mol (fold intact) + AlphaMissense 0.889 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframins fold survives this substitution ( $|\Delta\Delta G|=0.22$  kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.889. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.