

# WFS1 R138G — Wolframin

Arginine → Glycine at position 138. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance, AlphaMissense 0.609, DynaMut2  $\Delta\Delta G$  -1.06 kcal/mol (destabilising).

## IDENTITY

Variant	R138G (p.Arginine138Glycine)
DNA change	c.412C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV004201395
Amino acid change	Arginine (R) → Glycine (G)

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 138	<b>89.06</b> HIGH CONFIDENCE
Domain	N-terminal cytoplasmic (intrinsically disordered)
Position context	N-terminal cytoplasmic (intrinsically disordered)
IDR flag	No — pLDDT well above 50 threshold

Position 138 sits in N-terminal cytoplasmic (intrinsically disordered). The wild-type residue is positively charged (arginine — guanidinium, strong H-bond donor); 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

**0.609**am\_class: **likely pathogenic** —  
threshold > 0.564DYNAMUT2  $\Delta\Delta G$ **-1.06** kcal/molDestabilising · Job  
178092131018

PLDDT (ALPHAFOLD)

**89.06**

high confidence

## CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2025/08/31 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	R138G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) <ul style="list-style-type: none"><li>Inborn genetic diseases</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

$|\Delta\Delta G|=1.06 < 2$  kcal/mol (fold intact) + AlphaMissense 0.609 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframins fold survives this substitution ( $|\Delta\Delta G|=1.06$  kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.609. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.