

# WFS1 R177H — Wolframin

Arginine → Histidine at position 177. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance, AlphaMissense 0.854, DynaMut2  $\Delta\Delta G$  -1.11 kcal/mol (destabilising).

## IDENTITY

Variant	R177H (p.Arginine177Histidine)
DNA change	c.530G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001320924
Amino acid change	Arginine (R) → Histidine (H)

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 177	<b>90.81</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 177 sits in N-terminal cytoplasmic (intrinsically disordered). The wild-type residue is positively charged (arginine — guanidinium, strong H-bond donor); the mutant is titratable basic (histidine — imidazole). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.854**am\_class: **likely pathogenic** —  
threshold > 0.564DYNAMUT2  $\Delta\Delta G$ **-1.11** kcal/molDestabilising · Job  
178092112591

PLDDT (ALPHAFOLD)

**90.81**

high confidence

## CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2019/05/21 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	R177H 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

$|\Delta\Delta G|=1.11 < 2$  kcal/mol (fold intact) + AlphaMissense 0.854 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution ( $|\Delta\Delta G|=1.11$  kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.854. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.