

WFS1 R383P — Wolframin

Arginine → Proline at position 383. Transmembrane helix 3. ClinVar Uncertain significance, AlphaMissense 0.825, DynaMut2 $\Delta\Delta G$ +0.31 kcal/mol (stabilising).

IDENTITY

Variant	R383P (p.Arginine383Proline)
DNA change	c.1148G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002804379
Amino acid change	Arginine (R) → Proline (P)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 383	82.88 HIGH CONFIDENCE
Domain	Transmembrane helix 3
Position context	Inside Transmembrane helix 3 · position 383 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 383 sits in a transmembrane helix (Transmembrane helix 3). 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 positively charged (arginine — guanidinium, strong H-bond donor); the mutant is rigid/helix-breaking (proline — kinks backbone). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.825am_class: **likely pathogenic** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **0.31** kcal/mol

Stabilising · Job 178092113775

PLDDT (ALPHAFOLD)

82.88

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2023/01/10 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	R383P is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) <ul style="list-style-type: none">(no conditions catalogued)

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

$|\Delta\Delta G|=0.31 < 2$ kcal/mol (fold intact) + AlphaMissense 0.825 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframín's fold survives this substitution ($|\Delta\Delta G|=0.31$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.825. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.