

WFS1 P504R — Wolframin

Proline → Arginine at position 504. Transmembrane helix 7. ClinVar Uncertain significance, AlphaMissense 0.934, DynaMut2 $\Delta\Delta G$ -0.51 kcal/mol (destabilising).

IDENTITY

Variant	P504R (p.Proline504Arginine)
DNA change	c.1511C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001328269
Amino acid change	Proline (P) → Arginine (R)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 504	82.88 HIGH CONFIDENCE
Domain	Transmembrane helix 7
Position context	Inside Transmembrane helix 7 · position 504 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 504 sits in a transmembrane helix (Transmembrane helix 7). 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 rigid/helix-breaking (proline — kinks backbone); 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

0.934am_class: **likely pathogenic** — threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-0.51** kcal/mol

Destabilising · Job 178092144341

PLDDT (ALPHAFOLD)

82.88

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2022/08/08 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	P504R 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

$|\Delta\Delta G|=0.51 < 2$ kcal/mol (fold intact) + AlphaMissense 0.934 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframins fold survives this substitution ($|\Delta\Delta G|=0.51$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.934. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.