

WFS1 P533L — Wolframin

Proline → Leucine at position 533. Transmembrane helix 8. ClinVar Uncertain significance, AlphaMissense 0.978, DynaMut2 $\Delta\Delta G$ -0.01 kcal/mol (destabilising).

IDENTITY

Variant	P533L (p.Proline533Leucine)
DNA change	c.1598C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003338651
Amino acid change	Proline (P) → Leucine (L)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 533	84.00 HIGH CONFIDENCE
Domain	Transmembrane helix 8
Position context	Inside Transmembrane helix 8 · position 533 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 533 sits in a transmembrane helix (Transmembrane helix 8). 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 medium hydrophobic (leucine — branched). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.978

am_class: **likely pathogenic** —
threshold > 0.564

DYNAMUT2 $\Delta\Delta G$ **-0.01** kcal/mol

Destabilising · Job
178092093739

PLDDT (ALPHAFOLD)

84.00

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	1/01/01 00:00
Inheritance	Autosomal recessive Wolfram syndrome 1 phenotype documented.
WFS1 variant landscape	P533L is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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

$|\Delta\Delta G|=0.01 < 2$ kcal/mol (fold intact) + AlphaMissense 0.978 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution ($|\Delta\Delta G|=0.01$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.978. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.