

WFS1 L303P — Wolframin

Leucine → Proline at position 303. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance, AlphaMissense 0.990, DynaMut2 $\Delta\Delta G$ -0.14 kcal/mol (destabilising).

IDENTITY

| | |
|-------------------|-----------------------------|
| Variant | L303P (p.Leucine303Proline) |
| DNA change | c.908T>C |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV001317613 |
| Amino acid change | Leucine (L) → Proline (P) |

STRUCTURAL CONTEXT

| | |
|----------------------|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 303 | 67.88 CONFIDENT |
| Domain | N-terminal cytoplasmic (intrinsically disordered) |
| Position context | N-terminal cytoplasmic (intrinsically disordered) |
| IDR flag | No — pLDDT well above 50 threshold |

Position 303 sits in N-terminal cytoplasmic (intrinsically disordered). The wild-type residue is medium hydrophobic (leucine — branched); 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

0.990am_class: **likely pathogenic** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-0.14** kcal/molDestabilising · Job
178092088625

PLDDT (ALPHAFOLD)

67.88

confident

CLINICAL EVIDENCE

| | |
|------------------------|--|
| ClinVar classification | UNCERTAIN SIGNIFICANCE |
| Review status | criteria provided, single submitter |
| Last evaluated | 2020/09/11 00:00 |
| Inheritance | Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations. |
| WFS1 variant landscape | L303P 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

$|\Delta\Delta G|=0.14 < 2$ kcal/mol (fold intact) + AlphaMissense 0.990 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframins fold survives this substitution ($|\Delta\Delta G|=0.14$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.990. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.