

WFS1 A133V — Wolframin

Alanine → Valine at position 133. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance, AlphaMissense 0.941, DynaMut2 $\Delta\Delta G$ -0.51 kcal/mol (destabilising).

IDENTITY

| | |
|-------------------|----------------------------|
| Variant | A133V (p.Alanine133Valine) |
| DNA change | c.398C>T |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV003633039 |
| Amino acid change | Alanine (A) → Valine (V) |

STRUCTURAL CONTEXT

| | |
|----------------------|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 133 | 92.00 HIGH CONFIDENCE |
| Domain | N-terminal cytoplasmic (intrinsically disordered) |
| Position context | N-terminal cytoplasmic (intrinsically disordered) |
| IDR flag | No — pLDDT well above 50 threshold |

Position 133 sits in N-terminal cytoplasmic (intrinsically disordered). The wild-type residue is small/hydrophobic (alanine — methyl sidechain); the mutant is small hydrophobic (valine — branched). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.941am_class: **likely pathogenic** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-0.51** kcal/molDestabilising · Job
178092143075

PLDDT (ALPHAFOLD)

92.00

high confidence

CLINICAL EVIDENCE

| | |
|------------------------|--|
| ClinVar classification | UNCERTAIN SIGNIFICANCE |
| Review status | criteria provided, single submitter |
| Last evaluated | 2024/01/21 00:00 |
| Inheritance | Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations. |
| WFS1 variant landscape | A133V 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 0.941 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 0.941. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.