

WFS1 A307D — Wolframin

Alanine → Aspartic acid at position 307. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance, AlphaMissense 0.995, DynaMut2 $\Delta\Delta G$ -0.01 kcal/mol (destabilising).

IDENTITY

Variant	A307D (p.Alanine307Aspartic acid)
DNA change	c.920C>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001320779
Amino acid change	Alanine (A) → Aspartic acid (D)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 307	59.72 CONFIDENT
Domain	N-terminal cytoplasmic (intrinsically disordered)
Position context	N-terminal cytoplasmic (intrinsically disordered)
IDR flag	No — pLDDT well above 50 threshold

Position 307 sits in N-terminal cytoplasmic (intrinsically disordered). The wild-type residue is small/hydrophobic (alanine — methyl sidechain); the mutant is negatively charged (aspartate — carboxylate). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.995

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

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

Destabilising · Job
178092086702

PLDDT (ALPHAFOLD)

59.72

confident

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2021/04/27 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	A307D 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

$|\Delta\Delta G|=0.01 < 2$ kcal/mol (fold intact) + AlphaMissense 0.995 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 0.995. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.