

WFS1 V207F — Wolframin

Valine → Phenylalanine at position 207. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance, AlphaMissense 0.572, DynaMut2 $\Delta\Delta G$ -1.14 kcal/mol (destabilising).

IDENTITY

Variant	V207F (p.Valine207Phenylalanine)
DNA change	c.619G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003605481
Amino acid change	Valine (V) → Phenylalanine (F)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 207	62.16 CONFIDENT
Domain	N-terminal cytoplasmic (intrinsically disordered)
Position context	N-terminal cytoplasmic (intrinsically disordered)
IDR flag	No — pLDDT well above 50 threshold

Position 207 sits in N-terminal cytoplasmic (intrinsically disordered). The wild-type residue is small hydrophobic (valine — branched); the mutant is large aromatic hydrophobic (phenylalanine). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.572

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

DYNAMUT2 $\Delta\Delta G$ **-1.14** kcal/mol

Destabilising · Job
178092134928

PLDDT (ALPHAFOLD)

62.16

confident

CLINICAL EVIDENCE

ClinVar classification

UNCERTAIN SIGNIFICANCE

Review status	criteria provided, single submitter
Last evaluated	2024/08/14 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	V207F 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

$|\Delta\Delta G|=1.14 < 2$ kcal/mol (fold intact) + AlphaMissense 0.572 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframins fold survives this substitution ($|\Delta\Delta G|=1.14$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.572. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.