

WFS1 V176M — Wolframin

Valine → Methionine at position 176. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance, AlphaMissense 0.886, DynaMut2 $\Delta\Delta G$ -0.35 kcal/mol (destabilising).

IDENTITY

Variant	V176M (p.Valine176Methionine)
DNA change	c.526G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003469926
Amino acid change	Valine (V) → Methionine (M)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 176	88.88 HIGH CONFIDENCE
Domain	N-terminal cytoplasmic (intrinsically disordered)
Position context	N-terminal cytoplasmic (intrinsically disordered)
IDR flag	No — pLDDT well above 50 threshold

Position 176 sits in N-terminal cytoplasmic (intrinsically disordered). The wild-type residue is small hydrophobic (valine — branched); the mutant is hydrophobic sulfur (methionine). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.886am_class: **likely pathogenic** — threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-0.35** kcal/mol

Destabilising · Job 178092108671

PLDDT (ALPHAFOLD)

88.88

high confidence

CLINICAL EVIDENCE

ClinVar classification

UNCERTAIN SIGNIFICANCE

Review status	criteria provided, single submitter
Last evaluated	2024/09/08 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	V176M is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Inborn genetic diseases

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

$|\Delta\Delta G|=0.35 < 2$ kcal/mol (fold intact) + AlphaMissense 0.886 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframins fold survives this substitution ($|\Delta\Delta G|=0.35$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.886. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.