MOLECULAR ATLAS · VARIANT CARD

WFS1 V176A — Wolframin

Valine → Alanine at position 176. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance, AlphaMissense 0.878, DynaMut2 ΔΔG -1.37 kcal/mol (destabilising).

IDENTITY

Variant	V176A (p.Valine176Alanine)
DNA change	c.527T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001327312
Amino acid change	Valine (V) → Alanine (A)

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 small/hydrophobic (alanine — methyl sidechain). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.878

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

DYNAMUT2 ΔΔG

-1.37 kcal/mol

Destabilising · Job 178092109134

PLDDT (ALPHAFOLD)

88.88

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2026/01/02 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	V176A is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram-like syndrome
- Cataract 41
- Wolfram syndrome 1
- Autosomal dominant nonsyndromic hearing loss 6
- Type 2 diabetes mellitus

RESEARCH PATH DECISION TREE

```
ΔΔG < 2 + binding site affected → CATEGORY 3 — docking experiments ΔΔG 2–4 → CATEGORY
2 — pharmacological chaperones ΔΔG > 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

|ΔΔG|=1.37 < 2 kcal/mol (fold intact) + AlphaMissense 0.878 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=1.37 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.878. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
