MOLECULAR ATLAS · VARIANT CARD

WFS1 A519V — Wolframin

Alanine → Valine at position 519. Cytoplasmic loop 4. ClinVar Uncertain significance, AlphaMissense 0.713, DynaMut2 ΔΔG -1.03 kcal/mol (destabilising).

IDENTITY

Variant	A519V (p.Alanine519Valine)
DNA change	c.1556C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000166592
Amino acid change	Alanine (A) → Valine (V)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 519	**85.12** HIGH CONFIDENCE
Domain	Cytoplasmic loop 4
Position context	Loop region · position 519 sits between transmembrane segments, solvent-accessible
IDR flag	No — pLDDT well above 50 threshold

> Position 519 sits in a connecting loop between transmembrane helices. Loop residues are typically solvent-exposed and often contribute to interhelical contacts or serve as recognition sites for binding partners. 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

0.713

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

DYNAMUT2 ΔΔG

-1.03 kcal/mol

Destabilising · Job 178092153173

PLDDT (ALPHAFOLD)

85.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/06/22 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	A519V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

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

RESEARCH PATH DECISION TREE

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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
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Category 3/4 — Most Druggable

|ΔΔG|=1.03 < 2 kcal/mol (fold intact) + AlphaMissense 0.713 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=1.03 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.713. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.