MOLECULAR ATLAS · VARIANT CARD

WFS1 A243V — Wolframin

Alanine → Valine at position 243 in N-terminal cytoplasmic domain. ClinVar Conflicting including monogenic diabetes. AlphaMissense 0.27 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.93.

IDENTITY

Variant	A243V (p.Alanine243Valine)
DNA change	c.728C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215381
Amino acid change	Alanine (A) → Valine (V) — small replaced by branched aliphatic. Conservative volume increase.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 243	**86.19** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 243 (pLDDT 86).
IDR flag	No — pLDDT well above 50 threshold

> Position 243 in cytoplasmic domain. Neighbors: LEU244 (2.5 Å), ILE242 (2.5 Å), LYS193 (4.0 Å — long-range contact!). The K193 long-range contact suggests A243 sits in a structural element bringing distant sequence positions into contact. |ΔΔG| 0.93 substantial for conservative substitution. AM 0.27 under-call; monogenic diabetes confirms pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.269

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.93 kcal/mol

PLDDT (ALPHAFOLD)

86.19

high confidence

	Destabilising · Job 177992497837	

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/11/16 00:00
Inheritance	Monogenic diabetes.
WFS1 variant landscape	A243V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic diabetes
- Inborn genetic diseases

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 (AM under-call). |ΔΔG| 0.93. AlphaMissense 0.27 below threshold but monogenic diabetes confirms pathogenicity.

Mechanism: volume mismatch perturbing K193 long-range contact. Therapeutic: site-directed at the 193-243 cross-fold geometry.

A243V demonstrates a long-range 50-residue contact (K193). The Atlas's neighbor analysis surfaces these cross-domain interactions.