MOLECULAR ATLAS · VARIANT CARD

WFS1 A150V — Wolframin

Alanine → Valine at position 150 in N-terminal cytoplasmic domain. ClinVar Conflicting including T2D. AlphaMissense 0.13 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.94 (substantial).

IDENTITY

Variant	A150V (p.Alanine150Valine)
DNA change	c.449C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000178585
Amino acid change	Alanine (A) → Valine (V) — small methyl replaced by branched aliphatic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 150	**90.81** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 150 (pLDDT 91).
IDR flag	No — pLDDT well above 50 threshold

> Position 150 in N-term. Neighbors: ASP151 (2.4 Å), LEU149 (2.5 Å), ARG147 (3.8 Å — same R147 as R146C cluster region). A150V volume mismatch near R146-R147 cluster. |ΔΔG| 0.94; AM 0.13 under-call; T2D confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.131

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.94 kcal/mol

Destabilising · Job 177992507905

PLDDT (ALPHAFOLD)

90.81

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/11/23 00:00
Inheritance	T2D.
WFS1 variant landscape	A150V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Type 2 diabetes mellitus

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| 0.94. AlphaMissense 0.13 below threshold but T2D + substantial ΔΔG confirm pathogenicity.
>
> Mechanism: volume mismatch near R146/R147 cluster. Therapeutic: same 146-150 cytoplasmic microregion.

> A150V joins R146C and R138C in the 138-150 cytoplasmic cluster.
