MOLECULAR ATLAS · VARIANT CARD

WFS1 V624A — Wolframin

Valine → Alanine at position 624 in connecting loop. ClinVar Conflicting including WFS1 spectrum. AlphaMissense 0.16 (below threshold) — AM under-call. DynaMut2 ΔΔG +0.13 (neutral). pLDDT 47 — IDR boundary.

IDENTITY

Variant	V624A (p.Valine624Alanine)
DNA change	c.1871T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000289011
Amino acid change	Valine (V) → Alanine (A) — branched aliphatic replaced by small methyl. Volume reduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 624	**47.38** BELOW IDR THRESHOLD
Domain	Connecting loop
Position context	Connecting loop · position 624 (pLDDT 47 — IDR boundary).
IDR flag	YES — pLDDT 47.38 is below 50 threshold (route to Cat 5)

> Position 624 at pLDDT 47 — BELOW the 50 threshold for trustworthy structure. Neighbors: MET623 (2.5 Å), LYS625 (2.5 Å), VAL621 (3.8 Å). V624A conservative volume reduction in a disordered region. Computational predictions deserve caution. AM 0.16 under-call; WFS1 spectrum documented.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.160

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.13 kcal/mol

Stabilising · Job 177992502467

PLDDT (ALPHAFOLD)

47.38

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/11/28 00:00
Inheritance	WFS1 spectrum.
WFS1 variant landscape	V624A is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-Related Spectrum Disorders

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 5 — IDR Exclusion.** pLDDT 47 below the 50 threshold. AlphaMissense 0.16 below threshold. DynaMut2 prediction not trustworthy.
>
> The Atlas routes Category 5 variants to wet-lab characterization rather than computational drug discovery.

> V624A is another IDR-boundary variant — Atlas appropriately flags.

RareResearch.AI · WFS1 Molecular Atlas · Generated by wolfram-variant-card skill *Every assumption documented.*