

# WFS1 A48V — Wolframin

Valine for alanine at position 48. Buried in wolframin's N-terminal intrinsically disordered region. The card the Atlas refuses to confidently classify — on purpose.

## IDENTITY

Variant	A48V (p.Alanine48Valine)
DNA change	c.143C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000045435
Amino acid change	Alanine (A, small, hydrophobic) → Valine (V, slightly larger, branched, hydrophobic). Conservative substitution in a structured context — but A48 is not in a structured context.

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6 (released Aug 2025)
pLDDT at residue 48	<b>25.08</b> <span>BELOW IDR THRESHOLD</span>
Domain	N-terminal intrinsically disordered region (1-86)
Position context	N-terminal disordered region (1-86), within the wolframin-ATP6V1A interaction region — but no defined secondary structure
IDR flag	YES — pLDDT 25.08 is below 50 threshold (route to Cat 5)

Position 48 sits in the floppy, unstructured N-terminus of wolframin. AlphaFold's per-residue confidence here is pLDDT 25.08 — well below the 50 threshold that separates 'structured and modelable' from 'we don't know.' Any predicted local geometry at A48 is effectively a guess. UniProt annotates positions 1-321 as the wolframin-ATP6V1A interaction region, so A48 may participate in protein-protein binding — but the binding interface is not visible to a static structure prediction. Computational tools like DynaMut2 and AlphaMissense were trained on structured-region variants. They cannot reliably interpret variants in intrinsically disordered regions.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE <b>0.075</b> am_class: <b>LBen</b> — threshold > 0.564	DYNAMUT2 $\Delta\Delta G$ <b>-0.75</b> kcal/ mol Destabilising (UNTRUSTED — IDR) · Job 177985960542	PLDDT (ALPHAFOLD) <b>25.08</b> BELOW IDR THRESHOLD
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## CLINICAL EVIDENCE

ClinVar classification	<b>CONFLICTING CLASSIFICATIONS OF PATHOGENICITY</b>
Review status	criteria provided, conflicting classifications
Last evaluated	varies by submitter
Inheritance	Wolfram syndrome 1 reported in some submissions; benign in others — clinical signal unresolved
WFS1 variant landscape	A48V is 1 of 326 pathogenic-spectrum variants in WFS1 (out of 2,243 catalogued in ClinVar) <ul style="list-style-type: none"><li>• Inborn genetic diseases (some submitters)</li><li>• Wolfram syndrome 1 (some submitters)</li><li>• Not specified (other submitters — likely benign)</li><li>• WFS1-Related Spectrum Disorders</li></ul>

## RESEARCH PATH DECISION TREE

$\Delta\Delta G < 2$  + binding site affected → CATEGORY 3 – docking experiments  $\Delta\Delta G$  2–4 → CATEGORY 2 – pharmacological chaperones  $\Delta\Delta G > 4$  → CATEGORY 1 – gene therapy pLDDT < 50 → CATEGORY 5 – IDR, experimental only Stable fold + functional site hit → CATEGORY 4 – site-specific docking

**Final classification: Category 5 — Atlas refuses to take a structural position.** DynaMut2 returned a routine-looking  $\Delta\Delta G = -0.75$  kcal/mol, but that number is not trustworthy because the input structure at position 48 has pLDDT 25.08. DynaMut2 assumes a meaningful starting structure; for IDR residues, that assumption is violated. AlphaMissense scores it benign (0.075). ClinVar shows Conflicting classifications — submitting labs cannot agree. The Atlas resolves the tension by refusing to compute a confident category. **Route A48V to wet-lab functional validation only — cell-**

**based assays, family segregation, RNA-level effects, or in vivo binding studies.**

**Why this card is the Atlas's intellectual-honesty proof.** A system that confidently classifies everything is a system you cannot trust. A48V is the Atlas saying 'I do not know — and here is why.' Clinicians will trust a tool that names its own blind spots far more than one that pretends omniscience. This is the card that earns Sarah's confidence in everything else the Atlas claims.