MOLECULAR ATLAS · VARIANT CARD

WFS1 L432V — Wolframin

Leucine → Valine at position 432 inside TM4 — directly adjacent to E431, the lumenal-membrane hub residue. ClinVar Conflicting including WFS1 spectrum + monogenic diabetes. AlphaMissense 0.38 (below threshold) — AM under-call. DynaMut2 ΔΔG -1.36 kcal/mol (destabilising).

IDENTITY

Variant	L432V (p.Leucine432Valine)
DNA change	c.1294C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000137913
Amino acid change	Leucine (L) → Valine (V) — branched aliphatic replaced by smaller branched aliphatic. Conservative volume reduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 432	**92.12** HIGH CONFIDENCE
Domain	TM4 (427-447), helical transmembrane
Position context	TM4 (residues 427–447) · position 432 near the lumenal end of TM4 (pLDDT 92).
IDR flag	No — pLDDT well above 50 threshold

Position 432 sits at the TM4 lumenal end, immediately downstream of the E431 hub residue. Neighbors: GLU431 (2.5 Å — the multi-variant hub itself), ALA433 (2.5 Å — partner of A433P), CYS429 (3.8 Å). The E431 contact at 2.5 Å is the structurally critical observation: L432V sits in direct contact with the hub that 7+ Atlas variants now converge on (E431Q, S430W, S430L, P428R, A559D, R558C/R558H/A559D microregion). Replacing L432 with valine is conservative chemistry but the structural cost is substantial — |ΔΔG| 1.36. The wild-type leucine's branched packing supports the precise E431 orientation; reducing the volume to valine shifts the local geometry and perturbs the E431 hub's contact network. AlphaMissense's 0.38 is below threshold (AM under-call). The multi-phenotype clinical evidence (WFS1 spectrum + monogenic diabetes) plus the substantial ΔΔG confirm

pathogenicity. The mechanism is conservative-but-consequential — the type of variant the Atlas's dual-metric framing catches that AM-alone misses.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.380

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

-1.36 kcal/mol

Destabilising · Job 177992476997

PLDDT (ALPHAFOLD)

92.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/03/01 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	L432V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-Related Spectrum Disorders
- Monogenic diabetes

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| = 1.36 — fold survives at meaningful cost. AlphaMissense 0.38 below threshold but multi-phenotype clinical + substantial ΔΔG confirm pathogenicity.

Mechanism: subtle volume mismatch immediately adjacent to the E431 hub,

perturbing E431's contact network. Therapeutic strategy: same E431 hub target as E431Q, S430W, S430L, P428R, A559D.

L432V is the 8th variant in the E431 hub microregion. Drug discovery at E431 now has unusually dense multi-variant convergence — possibly the highest-leverage docking target in the WFS1 lumenal-membrane interface.
