MOLECULAR ATLAS · VARIANT CARD

WFS1 V871M — Wolframin

Valine → Methionine at position 871 inside TM11. ClinVar Conflicting including WFS1 spectrum + monogenic diabetes. AlphaMissense 0.14 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.15. Same position as V871G.

IDENTITY

Variant	V871M (p.Valine871Methionine)
DNA change	c.2611G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000095325
Amino acid change	Valine (V) → Methionine (M) — branched aliphatic replaced by flexible sulfur-containing hydrophobic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 871	**74.25** HIGH CONFIDENCE
Domain	TM11 (870-890), helical transmembrane
Position context	TM11 (residues 870–890) · position 871 (pLDDT 74). Same as V871G.
IDR flag	No — pLDDT well above 50 threshold

> Position 871 same neighbors as V871G: HIS872 (2.5 Å), THR870 (2.5 Å), TRP867 (3.7 Å). V871M conservative chemistry at the V871 position. AM 0.14 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.141

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.15 kcal/mol

Destabilising · Job 177992504902

PLDDT (ALPHAFOLD)

74.25

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	V871M 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 4 — Stable Fold, Function Disrupted (AM under-call). |ΔΔG| 0.15. AlphaMissense 0.14 below threshold but multi-phenotype confirms.

Mechanism: methionine chemistry shift at TM11 start. Therapeutic: same TM11 cluster.

V871M + V871G at same position — TM11 cluster continues to grow.