MOLECULAR ATLAS · VARIANT CARD

WFS1 V875M — Wolframin

Val→Met p875 TM11 AM=0.08 ddg=-0.11 pLDDT=82. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	V875M (p.Valine875Methionine)
DNA change	c.2623G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000259899
Amino acid change	methionine chemistry

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 875	**82.44** HIGH CONFIDENCE
Domain	TM11 (870-890), helical transmembrane
Position context	TM11 (870-890)
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: LYS876 (2.5 Å — K876T!), ALA874 (2.5 Å — A874T!), HIS872 (3.8 Å — V871G region). TM11 dense cluster. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.084

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.11 kcal/mol

Destabilising · Job 177992520647

PLDDT (ALPHAFOLD)

82.44

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/26 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	V875M is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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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Cat 4 — see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally identified. Therapeutic strategy: site-directed at contacts identified above, or wet-lab validation if pLDDT borderline/below 50.

TM11 cluster (now 7+ converging variants).
