MOLECULAR ATLAS · VARIANT CARD

WFS1 V601M — Wolframin

Val→Met p601 TM9 AM=0.07 ddg=-0.14 pLDDT=75. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	V601M (p.Valine601Methionine)
DNA change	c.1801G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215363
Amino acid change	methionine chemistry

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 601	**75.12** HIGH CONFIDENCE
Domain	TM9 (589-609), helical transmembrane
Position context	TM9 (589-609)
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: ALA602 (2.5 Å), THR600 (2.5 Å), ILE597 (3.8 Å — A598T region). TM9 cluster. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.069

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.14 kcal/mol

Destabilising · Job 177992526046

PLDDT (ALPHAFOLD)

75.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/11/19 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	V601M 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.

TM9 multi-variant cluster.
