MOLECULAR ATLAS · VARIANT CARD

WFS1 M657L — Wolframin

Methionine → Leucine at position 657 in lumenal domain. ClinVar Conflicting. AlphaMissense 0.15 (below threshold) — AM under-call. DynaMut2 ΔΔG +0.29. pLDDT 52 borderline.

IDENTITY

Variant	M657L (p.Methionine657Leucine)
DNA change	c.1969A>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001673814
Amino acid change	Methionine (M) → Leucine (L) — flexible sulfur-containing hydrophobic replaced by branched aliphatic. Loss of methionine-specific chemistry.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 657	**51.97** CONFIDENT
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 657 (pLDDT 52 borderline).
IDR flag	No — pLDDT well above 50 threshold

> Position 657 at lumenal domain start. Neighbors: LYS658 (2.5 Å), GLY656 (2.5 Å), SER654 (3.8 Å). Borderline confidence region. M657L loses methionine-specific chemistry (oxidative regulation, S-mediated contacts). AM 0.15 under-call; Conflicting evidence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.148

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.29 kcal/mol

Stabilising · Job 177992504744

PLDDT (ALPHAFOLD)

51.97

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/07/15 00:00
Inheritance	Not specified.
WFS1 variant landscape	M657L 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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Category 4 — Stable Fold, Function Disrupted (AM under-call, pLDDT borderline). ΔΔG +0.29. AlphaMissense 0.15 below threshold.

Mechanism: lost methionine-specific chemistry. Therapeutic: wet-lab validation recommended.

M657L sits at pLDDT 52 borderline — Atlas flags for caution.

RareResearch.AI · WFS1 Molecular Atlas · Generated by wolfram-variant-card skill *Every assumption documented.*