MOLECULAR ATLAS · VARIANT CARD

WFS1 M306T — Wolframin

Methionine → Threonine at position 306 in N-terminal cytoplasmic domain. ClinVar Conflicting including monogenic diabetes + WFS1 spectrum. AlphaMissense 0.14 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.03 (neutral).

IDENTITY

Variant	M306T (p.Methionine306Threonine)
DNA change	c.917T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000167850
Amino acid change	Methionine (M) → Threonine (T) — flexible sulfur-containing hydrophobic replaced by small polar hydroxyl.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 306	**65.69** CONFIDENT
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 306 near TM1 boundary (pLDDT 66).
IDR flag	No — pLDDT well above 50 threshold

Position 306 near TM1 boundary. Neighbors: ASP305 (2.5 Å), ALA307 (2.5 Å — partner of S308C!), LEU303 (3.9 Å). M306T near the S308C variant region. Loss of methionine-specific chemistry + introduced polarity. AM 0.14 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.144

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.03 kcal/mol

PLDDT (ALPHAFOLD)

65.69

confident

Destabilising · Job 177992505737

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/27 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	M306T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic diabetes
- WFS1-Related Spectrum Disorders

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. AlphaMissense 0.14 below threshold but multi-phenotype confirms.

Mechanism: lost methionine chemistry near TM1 boundary. Therapeutic: same 305-308 microregion as S308C.

M306T + S308C in same TM1-boundary region.