MOLECULAR ATLAS · VARIANT CARD

WFS1 T749M — Wolframin

Thr→Met p749 lumenal AM=0.09 ddg=+0.33 pLDDT=71. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	T749M (p.Threonine749Methionine)
DNA change	c.2246C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000906718
Amino acid change	polar→hydrophobic switch

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 749	**70.88** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: ALA750 (2.5 Å), SER748 (2.5 Å), THR747 (4.4 Å). Loss of H-bonding in polar microregion. The Atlas's neighbor extraction surfaces this variant's contacts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.093

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.33 kcal/mol

Stabilising · Job 177992515374

PLDDT (ALPHAFOLD)

70.88

high confidence

CLINICAL EVIDENCE

ClinVar classification	CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status	criteria provided, conflicting classifications
Last evaluated	2025/07/16 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	T749M 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 clear from neighbor analysis. Therapeutic strategy: site-directed at the contacts identified above.

Lumenal polar→hydrophobic switch.