MOLECULAR ATLAS · VARIANT CARD

WFS1 T699M — Wolframin

Threonine → Methionine at position 699 in lumenal domain. ClinVar Conflicting including monogenic hearing loss. AlphaMissense 0.603, ΔΔG +0.01 (neutral). Same position as T699P (Atlas card).

IDENTITY

Variant	T699M (p.Threonine699Methionine)
DNA change	c.2096C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000004522
Amino acid change	Threonine (T) → Methionine (M) — small polar hydroxyl replaced by flexible sulfur-containing hydrophobic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 699	**89.00** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 699 (pLDDT 89). Same as T699P.
IDR flag	No — pLDDT well above 50 threshold

Position 699 same neighbors as T699P: TRP700 (2.4 Å — Cat 2 outlier W700S region), VAL698 (2.5 Å), PHE825 (3.4 Å — W700-F825 π-stacking partner), SER826 (4.3 Å). T699M is the second pathogenic substitution at 699 (with T699P). Where T699P introduced a backbone kink, T699M conservatively swaps small polar for small hydrophobic. Both perturb the W700-F825 π-stacking geometry that pulls W700S into Cat 2 destabilization. ΔΔG neutral; AM 0.603 + monogenic hearing loss confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.603	**0.01** kcal/mol	**89.00**

am_class: **LPath** — threshold > 0.564	Stabilising · Job 177992467372	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/09/10 00:00
Inheritance	Monogenic hearing loss.
WFS1 variant landscape	T699M is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic hearing loss

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. ΔΔG ≈ 0. AlphaMissense 0.603 confirms severe consequence.

Mechanism: W700-F825 π-stacking perturbation via T699 contact.
Therapeutic: same W700-F825 microregion as T699P, W700C, W700S.

T699M + T699P + W700C + W700S — four Atlas variants converge on the W700-F825 π-stacking interface.