MOLECULAR ATLAS · VARIANT CARD

# WFS1 T699P — Wolframin

Threonine → Proline at position 699 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic for Wolfram syndrome 1. AlphaMissense 0.914, DynaMut2 ΔΔG -0.14 kcal/mol (mild destabilising). Proline-introduction adjacent to W700 (Cat 2 outlier region).

## IDENTITY

| | |
|---|---|
| Variant | T699P (p.Threonine699Proline) |
| DNA change | c.2095A>C |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV003767960 |
| Amino acid change | Threonine (T) → Proline (P) — small polar hydroxyl-bearing residue replaced by rigid helix-breaking residue. |

## STRUCTURAL CONTEXT

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|---|---|
| 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 in the ER lumen (pLDDT 89). Immediately adjacent to W700. |
| IDR flag | No — pLDDT well above 50 threshold |

Position 699 sits in wolframin's C-terminal lumenal domain, immediately preceding W700 (the position of W700S — Cat 2 outlier — and W700C in the Atlas). The AlphaFold model places T699 within 5 Å of TRP700 (2.4 Å), VAL698 (2.5 Å), PHE825 (3.4 Å — W700's aromatic-stacking partner), and SER826 (4.3 Å). The wild-type threonine at 699 sits in immediate contact with W700 and the F825 aromatic neighbor. The hydroxyl group H-bonds locally and stabilizes the geometry that supports W700's aromatic packing with F825. Replacing T699 with proline introduces a backbone kink immediately upstream of W700, perturbing the precise W700-F825 π-stacking geometry the Atlas's W700C card identifies as the key functional contact. The |ΔΔG| of 0.14 is small (fold absorbs), but the functional

consequence — disrupted W700 stacking — is the same severe pathogenic mechanism that pulls W700C into pathogenic territory.

## COMPUTATIONAL PREDICTIONS

| ALPHAMISSENSE | DYNAMUT2 ΔΔG | PLDDT (ALPHAFOLD) |
|---|---|---|
| **0.914** | **-0.14** kcal/mol | **89.00** |
| am_class: **LPath** — threshold > 0.564 | Destabilising · Job 177992005741 | high confidence |

## CLINICAL EVIDENCE

| | |
|---|---|
| ClinVar classification | **LIKELY PATHOGENIC** |
| Review status | criteria provided, single submitter |
| Last evaluated | 2025/01/27 00:00 |
| Inheritance | Wolfram syndrome 1 (AR) documented. |
| WFS1 variant landscape | T699P is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- Wolfram syndrome 1

## 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 3/4 — Most Druggable.** |ΔΔG| = 0.14 — fold survives. AlphaMissense 0.914 + Wolfram 1 confirm severe functional consequence.

Mechanism is backbone kink upstream of W700 that perturbs W700-F825 π-stacking geometry. Therapeutic strategy: same target as W700C/W700S — the W700-F825 aromatic stacking microregion.

> T699P, W700C, W700S all converge on the W700-F825 π-stacking interface — three Atlas variants at one therapeutic target. The Atlas surfaces these as a coherent multi-variant rescue opportunity.

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