MOLECULAR ATLAS · VARIANT CARD

WFS1 T321R — Wolframin

Threonine → Arginine at position 321 inside TM1. ClinVar Likely pathogenic. AlphaMissense 0.449 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.08 kcal/mol — essentially neutral.

IDENTITY

Variant	T321R (p.Threonine321Arginine)
DNA change	c.962C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001481097
Amino acid change	Threonine (T) → Arginine (R) — small polar hydroxyl replaced by large positively-charged guanidinium. Charge introduction into the bilayer.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 321	**75.12** HIGH CONFIDENCE
Domain	TM1 (314-334), helical transmembrane
Position context	TM1 (residues 314–334) · position 321 near the start of TM1 (pLDDT 75).
IDR flag	No — pLDDT well above 50 threshold

Position 321 sits in TM1, same neighbor environment as T321P (Atlas card adjacent): HIS322 (2.5 Å — partner of H323R and A326E Atlas cards through the H322-H323-A326 cluster), PRO320 (2.5 Å), ILE319 (3.8 Å), ILE324 (4.4 Å), HIS323 (4.5 Å). Replacing T321 with arginine introduces a large positive charge into the bilayer-embedded TM1. The arginine side chain likely extends toward the membrane-water interface. The H322-H323 cluster nearby is affected by the new positive charge. The |ΔΔG| of 0.08 (essentially zero) indicates fold accommodates the substitution. AlphaMissense's 0.449 is below threshold — AM under-call. ClinVar Likely Pathogenic establishes clinical relevance. T321R + T321P (same position, different chemistries) both pathogenic confirm position 321 as functionally important.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.449

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.08 kcal/mol

Destabilising · Job 177992011202

PLDDT (ALPHAFOLD)

75.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2025/08/12 00:00
Inheritance	Inheritance not specified.
WFS1 variant landscape	T321R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

RESEARCH PATH DECISION TREE

```
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
```

Category 4 — Stable Fold, Function Disrupted (AM under-call). |ΔΔG| = 0.08 — fold unchanged. AlphaMissense 0.449 below threshold.

Mechanism is charge introduction into TM1. Therapeutic strategy: TM1 microregion site-directed.

T321R + T321P together establish position 321 as a TM1 pathogenic hotspot. Both AM under-calls; both ClinVar pathogenic. Drug discovery here pauses for wet-lab work.