MOLECULAR ATLAS · VARIANT CARD

WFS1 T321P — Wolframin

Threonine → Proline at position 321 inside TM1. ClinVar Likely pathogenic. AlphaMissense 0.261 (below threshold) — AM under-call. DynaMut2 ΔΔG +0.13 kcal/mol — essentially neutral. Same position as T321R, proline-introduction at TM1 start.

IDENTITY

Variant	T321P (p.Threonine321Proline)
DNA change	c.961A>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000918064
Amino acid change	Threonine (T) → Proline (P) — small polar hydroxyl replaced by rigid helix-breaking residue.

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 at the start of TM1. Same neighbor environment as T321R: HIS322 (2.5 Å), PRO320 (2.5 Å — adjacent proline!), ILE319 (3.8 Å), ILE324 (4.4 Å), HIS323 (4.5 Å). Replacing T321 with proline creates a Pro-Pro motif (P320-P321) in the cytoplasmic-to-TM1 boundary region. Two adjacent prolines produce a rigid backbone segment with restricted conformational options — similar to the L723P/P724S Pro-Pro region in the lumenal domain. The ΔΔG of +0.13 (essentially neutral) reflects fold accommodation through local rearrangement. AlphaMissense's 0.261 below threshold is AM under-call. ClinVar Likely Pathogenic establishes clinical relevance.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.261

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.13 kcal/mol

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PLDDT (ALPHAFOLD)

75.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2025/03/10 00:00
Inheritance	Inheritance not specified.
WFS1 variant landscape	T321P 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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Category 4 — Stable Fold, Function Disrupted (AM under-call). ΔΔG = +0.13 — fold essentially unchanged. AlphaMissense 0.261 below threshold.

Mechanism is creation of a P320-P321 Pro-Pro motif at the TM1 boundary, altering TM1 insertion geometry. Therapeutic strategy: site-directed at TM1 start.

T321P + T321R both at position 321, both AM under-calls, both ClinVar pathogenic. The dense TM1 variant cluster (W314R, H313Y, T321R, T321P, H323R, A326E) makes TM1 a high-confidence multi-variant therapeutic target.