MOLECULAR ATLAS · VARIANT CARD

# **WFS1 T527I** — Wolframin

Threonine → Isoleucine at position 527 in connecting loop. ClinVar Conflicting including WFS1-related + DFNA6. AlphaMissense 0.12 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.53.

## IDENTITY

| | |
|---|---|
| Variant | T527I (p.Threonine527Isoleucine) |
| DNA change | c.1580C>T |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV000907533 |
| Amino acid change | Threonine (T) → Isoleucine (I) — polar hydroxyl replaced by branched aliphatic. Loss of H-bonding. |

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## STRUCTURAL CONTEXT

| | |
|---|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 527 | **78.50** HIGH CONFIDENCE |
| Domain | Connecting loop |
| Position context | Connecting loop · position 527 (pLDDT 78). |
| IDR flag | No — pLDDT well above 50 threshold |

> Position 527 in connecting loop near TM7 start (TM7 = 529-549). Neighbors: TYR528 (2.5 Å), GLY526 (2.5 Å), LEU531 (3.9 Å — same L531 in L543P TM7 region). T527I T→I substitution at the loop-TM7 boundary. AM 0.12 under-call; multi-phenotype confirms.

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## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.119**

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

**-0.53** kcal/mol

Destabilising · Job 177992508091

PLDDT (ALPHAFOLD)

**78.50**

high confidence

## CLINICAL EVIDENCE

| | |
|---|---|
| ClinVar classification | **CONFLICTING CLASSIFICATIONS OF PATHOGENICITY** |
| Review status | criteria provided, conflicting classifications |
| Last evaluated | 2025/09/27 00:00 |
| Inheritance | Multi-phenotype AD. |
| WFS1 variant landscape | T527I is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- WFS1-related disorder
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

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## 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 (AM under-call).** |ΔΔG| 0.53. AlphaMissense 0.12 below threshold but multi-phenotype confirms.

Mechanism: T→I lost H-bonding at TM7 boundary. Therapeutic: loop-TM7 boundary microregion.

T527I continues T→I class (with T337I, T361I, T361S, T461I).

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RareResearch.AI · WFS1 Molecular Atlas · Generated by wolfram-variant-card skill

*Every assumption documented.*