MOLECULAR ATLAS · VARIANT CARD

# WFS1 C541W — Wolframin

Cysteine → Tryptophan at position 541 inside TM7. ClinVar Conflicting including Wolfram. AlphaMissense 0.657, ΔΔG -1.54.

## IDENTITY

| | |
|---|---|
| Variant | C541W (p.Cysteine541Tryptophan) |
| DNA change | c.1623T>G |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV001046024 |
| Amino acid change | Cysteine (C) → Tryptophan (W) — small thiol replaced by bulky aromatic indole. Massive volume increase + loss of disulfide potential. |

## STRUCTURAL CONTEXT

| | |
|---|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 541 | **90.12** HIGH CONFIDENCE |
| Domain | TM7 (529-549), helical transmembrane |
| Position context | TM7 (residues 529–549) · position 541 (pLDDT 90). |
| IDR flag | No — pLDDT well above 50 threshold |

Position 541 in TM7 (same broader region as L543P, L543F). Neighbors: TRP540 (2.5 Å — adjacent existing tryptophan!), GLU542 (2.5 Å), THR440 (3.4 Å — TM4-TM7 cross-helix!), PHE538 (3.5 Å). The wild-type C541 is a small thiol in a bilayer-embedded position with aromatic neighbor (W540) and TM4 cross-contact (T440). Replacing it with tryptophan adds massive aromatic volume — creating W540-W541 tandem tryptophan motif. |ΔΔG| 1.54 substantial. AM 0.657 + Wolfram confirm severe consequence.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.657**

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

PLDDT (ALPHAFOLD)

**90.12**

high confidence

**-1.54** kcal/mol

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## CLINICAL EVIDENCE

| | |
|---|---|
| ClinVar classification | **CONFLICTING CLASSIFICATIONS OF PATHOGENICITY** |
| Review status | criteria provided, conflicting classifications |
| Last evaluated | 2023/05/23 00:00 |
| Inheritance | Wolfram syndrome 1. |
| WFS1 variant landscape | C541W is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- Wolfram syndrome 1
- Inborn genetic diseases

## 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| = 1.54. AlphaMissense 0.657 + Wolfram confirm severe consequence.

Mechanism: tandem tryptophan motif creation + TM4-TM7 cross-helix disruption at T440. Therapeutic: TM4-TM7 interface site-directed.

C541W identifies a TM4-TM7 cross-helix contact at T440 — adding to the F408 (TM3-TM7) and S444/S551 (TM4-TM7) cross-helix targets.