MOLECULAR ATLAS · VARIANT CARD

# WFS1 C360R — Wolframin

Cysteine → Arginine at position 360. Transmembrane helix 2. ClinVar Uncertain significance, AlphaMissense 0.994, DynaMut2 ΔΔG -1.42 kcal/mol (destabilising).

## IDENTITY

| | |
|---|---|
| Variant | C360R (p.Cysteine360Arginine) |
| DNA change | c.1078T>C |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV002790627 |
| Amino acid change | Cysteine (C) → Arginine (R) |

## STRUCTURAL CONTEXT

| | |
|---|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 360 | **90.12** HIGH CONFIDENCE |
| Domain | Transmembrane helix 2 |
| Position context | Inside Transmembrane helix 2 · position 360 is bilayer-embedded |
| IDR flag | No — pLDDT well above 50 threshold |

> Position 360 sits in a transmembrane helix (Transmembrane helix 2). Wolframin has eleven such helices anchoring it in the ER membrane; substitutions inside the bilayer-embedded segments can disrupt helix packing, lipid contacts, and the overall ER topology of the protein. The wild-type residue is thiol (cysteine — disulfide-capable, free -SH); the mutant is positively charged (arginine — guanidinium, strong H-bond donor). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.994**

am_class: **likely pathogenic** — threshold > 0.564

DYNAMUT2 ΔΔG

**-1.42** kcal/mol

Destabilising · Job 178092137123

PLDDT (ALPHAFOLD)

**90.12**

high confidence

## CLINICAL EVIDENCE

| | |
|---|---|
| ClinVar classification | UNCERTAIN SIGNIFICANCE |
| Review status | criteria provided, multiple submitters, no conflicts |
| Last evaluated | 2024/02/09 00:00 |
| Inheritance | Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations. |
| WFS1 variant landscape | C360R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- (no 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 3/4 — Most Druggable**

|ΔΔG|=1.42 < 2 kcal/mol (fold intact) + AlphaMissense 0.994 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=1.42 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.994. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.

---