MOLECULAR ATLAS · VARIANT CARD

WFS1 W540C — Wolframin

Tryptophan → Cysteine at position 540. Transmembrane helix 8. ClinVar Uncertain significance, AlphaMissense 0.996, DynaMut2 ΔΔG -1.06 kcal/mol (destabilising).

IDENTITY

Variant	W540C (p.Tryptophan540Cysteine)
DNA change	c.1620G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001803909
Amino acid change	Tryptophan (W) → Cysteine (C)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 540	**93.38** HIGH CONFIDENCE
Domain	Transmembrane helix 8
Position context	Inside Transmembrane helix 8 · position 540 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

> Position 540 sits in a transmembrane helix (Transmembrane helix 8). 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 bulky aromatic (tryptophan — indole ring); the mutant is thiol (cysteine — disulfide-capable, free -SH). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.996

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

DYNAMUT2 ΔΔG

-1.06 kcal/mol

Destabilising · Job 178092086312

PLDDT (ALPHAFOLD)

93.38

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2020/11/02 00:00
Inheritance	Autosomal recessive Wolfram syndrome 1 phenotype documented.
WFS1 variant landscape	W540C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram-like syndrome
- Wolfram syndrome 1

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|=1.06 < 2 kcal/mol (fold intact) + AlphaMissense 0.996 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=1.06 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.996. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.