MOLECULAR ATLAS · VARIANT CARD

WFS1 C537Y — Wolframin

Cysteine → Tyrosine at position 537. Transmembrane helix 8. ClinVar Uncertain significance, AlphaMissense 0.986, DynaMut2 ΔΔG -1.43 kcal/mol (destabilising).

IDENTITY

Variant	C537Y (p.Cysteine537Tyrosine)
DNA change	c.1610G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215390
Amino acid change	Cysteine (C) → Tyrosine (Y)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 537	**89.50** HIGH CONFIDENCE
Domain	Transmembrane helix 8
Position context	Inside Transmembrane helix 8 · position 537 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 537 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 thiol (cysteine — disulfide-capable, free -SH); the mutant is aromatic with hydroxyl (tyrosine — H-bond donor/acceptor). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.986

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

DYNAMUT2 ΔΔG

-1.43 kcal/mol

Destabilising · Job 178092090125

PLDDT (ALPHAFOLD)

89.50

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/12/26 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	C537Y is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Inborn genetic diseases
- Monogenic diabetes
- Cataract 41
- Autosomal dominant nonsyndromic hearing loss 6
- Type 2 diabetes mellitus
- Wolfram syndrome 1
- Wolfram-like syndrome

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|=1.43 < 2 kcal/mol (fold intact) + AlphaMissense 0.986 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=1.43 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.986. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
