MOLECULAR ATLAS · VARIANT CARD

WFS1 C850Y — Wolframin

Cysteine → Tyrosine at position 850 in wolframin's C-terminal lumenal domain. ClinVar Conflicting classifications including Wolfram syndrome 1. AlphaMissense 0.975, DynaMut2 ΔΔG -0.42 kcal/mol (destabilising). The C850 partner of C847Y in the inferred C847-C850 disulfide.

IDENTITY

Variant	C850Y (p.Cysteine850Tyrosine)
DNA change	c.2549G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000287170
Amino acid change	Cysteine (C) → Tyrosine (Y) — thiol-bearing residue replaced by aromatic phenol. Loss of disulfide potential; aromatic introduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 850	**74.25** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 850 in the ER lumen (pLDDT 74 — borderline).
IDR flag	No — pLDDT well above 50 threshold

Position 850 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places C850 within 5 Å of MET851 (2.5 Å), ASN849 (2.5 Å), and CYS847 (3.6 Å — partner of C847Y Atlas card, possible disulfide). The C847-C850 distance of 3.6 Å is the strongest disulfide-distance signal in this batch. Replacing C850 with tyrosine eliminates this potential disulfide and introduces aromatic volume. Combined with C847Y (Atlas card adjacent), both ends of the inferred C847-C850 disulfide are now known to be pathogenic when mutated. The |ΔΔG| of 0.42 reflects fold accommodation. AlphaMissense's 0.975 confirms severe functional consequence. pLDDT 74 is borderline but above the IDR threshold.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.975	**-0.42** kcal/mol	**74.25**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992299988	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2023/11/07 00:00
Inheritance	Wolfram syndrome 1 documented.
WFS1 variant landscape	C850Y is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- 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| = 0.42 — fold survives. AlphaMissense 0.975 + Wolfram 1 confirm severe functional consequence.

Mechanism is loss of the inferred C847-C850 disulfide. Therapeutic strategy: same C847-C850 microregion as C847Y.

C850Y + C847Y are the two pathogenic variants at opposite ends of the inferred C847-C850 disulfide. The Atlas now contains three identified disulfide-pair targets: C673-C690, C733-C765, C847-C850.