MOLECULAR ATLAS · VARIANT CARD

WFS1 C847Y — Wolframin

Cysteine → Tyrosine at position 847 in wolframin's C-terminal lumenal domain. ClinVar Conflicting classifications including Wolfram syndrome 1 and autistic behavior. AlphaMissense 0.994 (near-maximum), DynaMut2 ΔΔG -0.92 kcal/mol (destabilising). Cysteine-removal with potential disulfide loss to C850.

IDENTITY

Variant	C847Y (p.Cysteine847Tyrosine)
DNA change	c.2540G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000437421
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 847	**86.19** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 847 in the ER lumen (pLDDT 86).
IDR flag	No — pLDDT well above 50 threshold

Position 847 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places C847 within 5 Å of SER846 (2.4 Å), LEU848 (2.5 Å), LEU822 (3.8 Å — long-range), ILE823 (4.3 Å), and CYS850 (4.4 Å — another cysteine!). The C847-C850 distance of 4.4 Å is consistent with a possible structural disulfide bond. Replacing C847 with tyrosine eliminates this potential disulfide and introduces aromatic volume. The C850 partner residue (partner of C850Y Atlas card) loses its disulfide partner if one existed. The |ΔΔG| of 0.92 reflects substantial fold cost. AlphaMissense 0.994 confirms severe functional consequence. The C847-C850 microregion has variants at both cysteines (C847Y and C850Y), suggesting both cysteines are structurally important and disulfide-related.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.994	**-0.92** kcal/mol	**86.19**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992012957	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2024/07/05 00:00
Inheritance	Conflicting classifications including Wolfram syndrome 1.
WFS1 variant landscape	C847Y is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1
- Autistic behavior

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| = 0.92 — fold survives. AlphaMissense 0.994 confirms severe functional consequence.

Mechanism is potential C847-C850 disulfide loss plus aromatic volume introduction. Therapeutic strategy: site-directed at the C847-C850 microregion.

C847Y + C850Y are sister variants at adjacent cysteines, possibly a structural disulfide pair. The Atlas now identifies THREE possible disulfide

pairs in the lumenal domain: C673-C690, C733-C765, C847-C850. The lumenal fold appears to rely on multiple disulfides for structural integrity.
