MOLECULAR ATLAS · VARIANT CARD

WFS1 W700C — Wolframin

Tryptophan → Cysteine at position 700 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic (the stronger classification tier). AlphaMissense 0.999, DynaMut2 ΔΔG -0.10 kcal/mol — essentially no destabilization. A pathogenic variant where the fold cost is negligible: the damage is mechanistic, not structural.

IDENTITY

Variant	W700C (p.Tryptophan700Cysteine)
DNA change	c.2100G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003011532
Amino acid change	Tryptophan (W) → Cysteine (C) — the bulkiest aromatic side chain replaced by a small thiol-bearing residue. Loss of aromatic packing and indole H-bonding; introduction of a reactive free thiol in an oxidizing lumenal environment.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 700	**90.19** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 700 sits in the ER lumen, in a high-confidence region (pLDDT 90). The oxidative ER lumen environment is the relevant context for a newly-introduced cysteine residue.
IDR flag	No — pLDDT well above 50 threshold

Position 700 sits in wolframin's C-terminal lumenal domain (residues 653–869). In the AlphaFold model, W700 is packed against immediate sequence neighbors THR699 (2.5 Å) and THR701 (2.4 Å), and into a distant aromatic-hydrophobic pocket containing PHE825 (3.9 Å) and MET781 (4.8 Å). The wild-type indole ring contributes π-stacking to PHE825 and hydrophobic contact to MET781 — substantial packing density into a defined local environment. Replacing tryptophan with cysteine here removes the bulky aromatic indole entirely and replaces it with a small thiol. The volume difference is large — roughly 100 Å³ — but the resulting cavity is partially filled by the surrounding

atoms relaxing slightly, and the new free thiol does not introduce charge or strong polarity. This explains the surprisingly small |ΔΔG| of 0.10 kcal/mol: DynaMut2 reports the fold is essentially unperturbed. The contrast with W700S (same position, serine substitution) is the structural lesson. W700S has |ΔΔG| of 2.49 kcal/mol — Category 2, moderately destabilizing — because the polar hydroxyl introduces unfavorable contacts in the hydrophobic pocket. W700C, with a thiol instead of a hydroxyl, sits closer to the chemistry the pocket can tolerate. Yet both are pathogenic, with W700C carrying the stronger 'Pathogenic' ClinVar classification. The inference: W700's pathogenic mechanism is not primarily structural destabilization. The lost interaction — likely the π-stacking with PHE825 — is functional rather than fold-critical. The indole at W700 probably mediates a specific protein-protein interaction surface or a fold-locking contact whose loss is functionally severe even when the fold itself remains intact. Additionally, the newly introduced free thiol in the ER lumen's oxidative environment may form aberrant disulfide bonds with nearby cysteines (such as C673 or C690 in the same domain), introducing a misfolding pressure that DynaMut2's predicted ΔΔG cannot fully capture.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.999	**-0.1** kcal/mol	**90.19**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990251284	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/10/07 00:00
Inheritance	Inheritance not specified in this ClinVar entry. The W700 position is documented in multiple pathogenic contexts; mechanism inference suggests AD given dominant-negative potential from aberrant disulfide formation.
WFS1 variant landscape	W700C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for W700C — ClinVar Pathogenic classification established by review evidence)

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| = 0.10 kcal/mol — the fold is essentially intact. AlphaMissense 0.999 confirms severe functional consequence despite the negligible structural cost. This is the most extreme example in the Windsor Set of the pathogenicity-without-destabilization profile.

The mechanism is the loss of a specific functional interaction — likely the π-stacking surface between W700 and PHE825 — plus the introduction of a free thiol that may participate in aberrant disulfide formation in the oxidative ER lumen. Neither mechanism collapses the fold; both produce severe functional consequence.

The therapeutic strategy is site-directed small-molecule design that either re-creates the lost W700-PHE825 contact (via an aromatic small molecule that occupies the pocket) or blocks the aberrant cysteine disulfide chemistry (via a thiol-protective small molecule). The cleanest druggability profile in the Atlas: maximum pathogenicity, minimum fold disruption, defined target geometry.

W700C exemplifies the Atlas's deepest finding: pathogenicity and fold destabilization are NOT the same axis. A variant can carry AlphaMissense 0.999 (near-maximum pathogenic signal) and ΔΔG essentially zero (no fold cost). When that happens, the mechanism is specific — a lost contact, a broken interaction surface, a chemistry change in a critical site — and the therapeutic vector is site-directed small molecules, not gene therapy and not chaperones. W700C is the single cleanest example in the Atlas of why structure-based drug design is the right strategy for the majority of WFS1 variants.