MOLECULAR ATLAS · VARIANT CARD

# WFS1 W700S — Wolframin

Tryptophan → Serine at position 700 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic. AlphaMissense 0.996 (deeply pathogenic), DynaMut2 ΔΔG -2.49 kcal/mol (destabilising). Together with V779G, the second of only two Cat 2 variants in the entire 245-variant Atlas.

## IDENTITY

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|---|---|
| Variant | W700S (p.Tryptophan700Serine) |
| DNA change | c.2099G>C |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV004802689 |
| Amino acid change | Tryptophan (W) → Serine (S) — the bulkiest aromatic side chain in the genetic code replaced by a small polar hydroxyl. The volume difference is dramatic. |

## STRUCTURAL CONTEXT

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|---|---|
| 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 lies inside the ER lumen, in a high-confidence region of the AlphaFold model (pLDDT 90). |
| IDR flag | No — pLDDT well above 50 threshold |

Position 700 sits in wolframin's C-terminal lumenal domain (residues 653–869), the protein's largest soluble region and the documented site of partner interactions with ATF6 (the master regulator of the unfolded protein response) and the Na+/K+ ATPase β1 subunit. The AlphaFold model shows W700 packed against immediate sequence neighbors THR699 (2.5 Å) and THR701 (2.4 Å), and into a distant hydrophobic pocket containing PHE825 (3.9 Å) and MET781 (4.8 Å). The aromatic indole ring of tryptophan provides a substantial hydrophobic contact surface against PHE825 — likely a π-stacking or edge-face aromatic interaction — and into the lipid-like pocket lined by methionine. Replacing tryptophan with serine at this position removes the indole ring entirely and replaces it with a small polar hydroxyl. The volume loss is approximately 130 Å³ — among the largest single-

substitution volume losses possible in protein chemistry. The π-stacking interaction with PHE825 is eliminated, the hydrophobic contact to MET781 is broken, and the resulting cavity is too large to be filled by side-chain repacking. The introduced hydroxyl group is polar and small, and would prefer to point toward solvent rather than into the hydrophobic pocket — further destabilizing the local fold. DynaMut2 returns |ΔΔG| = 2.49 kcal/mol, placing W700S in Category 2 — moderately destabilizing but not gross-misfolding. The fold survives but is energetically compromised in proportion to the lost hydrophobic packing. Note that the W700C variant at the same position (Atlas card adjacent) shows |ΔΔG| of only -0.10 kcal/mol — replacing the indole with a thiol preserves more volume than replacing it with a hydroxyl, even though both are small polar groups. This W → C vs W → S contrast is a clean local example of how packing density, not just chemical class, drives WFS1 destabilization.

## COMPUTATIONAL PREDICTIONS

| ALPHAMISSENSE | DYNAMUT2 ΔΔG | PLDDT (ALPHAFOLD) |
|---|---|---|
| **0.996** | **-2.49** kcal/mol | **90.19** |
| am_class: **LPath** — threshold > 0.564 | Destabilising · Job 177991410657 | high confidence |

## CLINICAL EVIDENCE

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|---|---|
| ClinVar classification | **LIKELY PATHOGENIC** |
| Review status | criteria provided, single submitter |
| Last evaluated | 2025/02/27 00:00 |
| Inheritance | Inheritance pattern not specified in this ClinVar entry. WFS1 supports both autosomal dominant (DFNA6/14/38, Wolfram-like syndrome) and autosomal recessive (classical Wolfram syndrome) presentations; the W700 position appears in both contexts depending on the substituting residue. |
| WFS1 variant landscape | W700S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- (no specific conditions catalogued for W700S — ClinVar Likely 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 2 — Moderately Destabilizing.** |ΔΔG| = 2.49 kcal/mol places W700S just inside the moderately destabilizing range. The fold survives but a fraction of translated protein will be cleared by ER quality control before reaching its functional location.

This is a pharmacological chaperone candidate. The lost stability comes from a volume mismatch in a packed hydrophobic pocket — not from a broken specific bond or a disrupted catalytic site. The right intervention is a small molecule that stabilizes the wolframin fold globally, shifting the folding equilibrium toward functional protein. The CFTR-corrector analogy applies: rescue the folding yield, not the function.

Worth noting alongside the W700C card: W700 itself sits in a position where multiple pathogenic substitutions are documented, with substitution chemistry directly controlling severity. This makes W700 a useful didactic example of why structural context matters more than the position label alone — the variant cards must always be read at the specific substitution level.

W700S is one of two variants out of 245 in the Atlas where |ΔΔG| exceeds 2 kcal/mol. Both outliers stop well short of the 4 kcal/mol gross-misfolding threshold. The Atlas-wide finding holds: WFS1 pathogenic variants do not require gene therapy. They damage the fold in measurable but tractable ways. W700S adds nuance to that picture — even within a single position, the substitution chemistry determines whether the variant is mildly perturbing (W700C, |ΔΔG| 0.1) or moderately destabilizing (W700S, |ΔΔG| 2.5). The Atlas captures that resolution.