MOLECULAR ATLAS · VARIANT CARD

# WFS1 W700R — Wolframin

Tryptophan → Arginine at position 700. C-terminal ER-lumenal (calcium binding. ClinVar Uncertain significance, AlphaMissense 1.000, DynaMut2 ΔΔG -2.17 kcal/mol (destabilising).

## IDENTITY

| | |
|---|---|
| Variant | W700R (p.Tryptophan700Arginine) |
| DNA change | c.2098T>A |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV002637634 |
| Amino acid change | Tryptophan (W) → Arginine (R) |

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## STRUCTURAL CONTEXT

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|---|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 700 | **90.19** HIGH CONFIDENCE |
| Domain | C-terminal ER-lumenal (calcium binding, calmodulin, chaperone) |
| Position context | C-terminal lumenal domain · position 700 projects into the ER lumen |
| IDR flag | No — pLDDT well above 50 threshold |

> Position 700 sits in the C-terminal lumenal domain (residues 653–869), wolframin's largest soluble region. This domain projects into the ER lumen and is implicated in calcium handling, ER stress sensing, and protein–protein interactions with ATF6 and Na+/K+ ATPase β1. The wild-type residue is bulky aromatic (tryptophan — indole ring); the mutant is positively charged (arginine — guanidinium, strong H-bond donor). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

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## COMPUTATIONAL PREDICTIONS

| ALPHAMISSENSE | DYNAMUT2 ΔΔG | PLDDT (ALPHAFOLD) |
|---|---|---|
| **1.000** | **-2.17** kcal/mol | **90.19** |
| am_class: **likely pathogenic** — threshold > 0.564 | Destabilising · Job 178090203217 | high confidence |

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## CLINICAL EVIDENCE

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|---|---|
| ClinVar classification | **UNCERTAIN SIGNIFICANCE** |
| Review status | criteria provided, single submitter |
| Last evaluated | 2023/10/09 00:00 |
| Inheritance | Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations. |
| WFS1 variant landscape | W700R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- (no conditions catalogued)

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## 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**

$|\Delta\Delta G|=2.17$ in the 2–4 range. Pharmacological chaperone candidate.

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