MOLECULAR ATLAS · VARIANT CARD

# WFS1 C690R — Wolframin

Cysteine → Arginine at position 690 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic. AlphaMissense 1.000 — the maximum possible pathogenicity score — paired with DynaMut2 ΔΔG of -1.29 kcal/mol (destabilising). High pathogenic confidence with a fold-intact mechanism.

## IDENTITY

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|---|---|
| Variant | C690R (p.Cysteine690Arginine) |
| DNA change | c.2068T>C |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV002203528 |
| Amino acid change | Cysteine (C) → Arginine (R) — a thiol-bearing residue, capable of forming structural disulfide bonds, replaced by a large positively-charged guanidinium-bearing residue. Loss of disulfide potential and introduction of bulk charge. |

## STRUCTURAL CONTEXT

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|---|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 690 | **90.69** HIGH CONFIDENCE |
| Domain | C-terminal lumenal domain (653-869) |
| Position context | C-terminal lumenal domain · position 690 sits in the ER lumen, in a well-folded region (pLDDT 91). The ER lumen is an oxidizing environment that supports disulfide bond formation — a context where cysteine residues frequently play structural roles. |
| IDR flag | No — pLDDT well above 50 threshold |

Position 690 sits in wolframin's C-terminal lumenal domain (residues 653–869). The ER lumen is the cell's primary oxidative folding compartment, and cysteine residues in lumenal domains commonly form structural disulfide bonds that lock the fold. The AlphaFold model places C690 within 5 Å of: LEU689 (2.5 Å) and SER691 (2.5 Å) as immediate sequence neighbors, but critically, also within 3.8 Å of CYS673 — another cysteine in the same domain. This proximity to CYS673 is the key structural observation. A 3.8 Å Cα-to-CA distance between two cysteines is consistent with — though not definitive proof of — a disulfide bond connecting these two residues (typical

Cys-Cys disulfides span 4.5-6.5 Å between Cα atoms; AlphaFold's modeling of disulfides is approximate but the spatial relationship is informative). If C690 and C673 form a structural disulfide in the lumenal fold, the C690R substitution destroys that bond entirely. Arginine cannot replicate the covalent crosslink. Additionally, the substitution introduces a large positively charged guanidinium group into a position that previously held a small thiol. The surrounding lumenal environment (THR686, GLN687, HIS692, ILE688, LEU833 all within 5 Å) is mostly polar to neutral; introducing a charge here will reorganize the local hydrogen-bond network and the local electrostatics. The combined effect — disulfide loss plus charge introduction — produces |ΔΔG| of 1.29 kcal/mol. Notably modest given how disruptive the chemistry is, which suggests the fold has slack to absorb the perturbation, but the AlphaMissense score of 1.000 indicates the functional consequence is severe even if the global fold tolerates it.

## COMPUTATIONAL PREDICTIONS

| ALPHAMISSENSE | DYNAMUT2 ΔΔG | PLDDT (ALPHAFOLD) |
|---|---|---|
| **1.000** | **-1.29** kcal/mol | **90.69** |
| am_class: **LPath** — threshold > 0.564 | Destabilising · Job 177991412857 | high confidence |

## CLINICAL EVIDENCE

| | |
|---|---|
| ClinVar classification | **LIKELY PATHOGENIC** |
| Review status | criteria provided, single submitter |
| Last evaluated | 2022/04/18 00:00 |
| Inheritance | Inheritance not specified for this entry. C690R has the AlphaMissense and ClinVar profile of a severe pathogenic variant; functional context will determine whether it falls into the AR Wolfram syndrome 1 or AD Wolfram-like syndrome category. |
| WFS1 variant landscape | C690R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- (no specific conditions catalogued for C690R — Likely pathogenic by ClinVar 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| = 1.29 kcal/mol is well below the 2 kcal/mol fold-integrity threshold. The wolframin fold survives. AlphaMissense 1.000 (the maximum possible score) confirms severe functional consequence despite the modest structural cost.

The mechanism is a broken specific interaction — likely a structural disulfide between C690 and C673 plus disrupted local electrostatics — rather than global unfolding. This is the highest-priority druggability profile in the Atlas. The therapeutic strategy is site-directed: small molecules that re-stabilize the disrupted C673-C690 region of the lumenal fold, or that compensate for the lost crosslink by occupying the resulting cavity. Pharmacological chaperone screening with the WFS1 lumenal domain in folded form is the natural starting assay.

Gene therapy is unnecessary and likely contraindicated: the protein is folding, the variant is producing a measurable functional defect at a defined site, and that site is the rational target.

C690R is one of the cleanest examples in the Atlas of the central thesis: maximum AlphaMissense pathogenicity (1.000) paired with a small structural cost (|ΔΔG| 1.29). The mutation breaks a specific local interaction — almost certainly a disulfide — and that local damage produces severe functional consequence without collapsing the protein. This is exactly the variant profile where site-directed small-molecule therapy is the correct vector. It is also a case where the structural reasoning is unusually clean: the proximity of C690 to C673 in the AlphaFold model gives drug designers a specific target geometry to work with.