MOLECULAR ATLAS · VARIANT CARD

WFS1 C733G — Wolframin

Cysteine → Glycine at position 733 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic for Wolfram syndrome 1. AlphaMissense 0.912, DynaMut2 ΔΔG -1.15 kcal/mol (destabilising). Cysteine-removal variant with potential disulfide partner C765 in spatial proximity.

IDENTITY

Variant	C733G (p.Cysteine733Glycine)
DNA change	c.2197T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001264333
Amino acid change	Cysteine (C) → Glycine (G) — thiol-bearing residue replaced by smallest amino acid. Loss of disulfide-bond potential plus loss of side chain entirely.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 733	**88.50** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 733 in the ER lumen (pLDDT 88).
IDR flag	No — pLDDT well above 50 threshold

Position 733 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places C733 within 5 Å of ARG732 (2.4 Å — same R732 as G736R neighbor), LEU734 (2.5 Å), CYS765 (3.5 Å — possible disulfide partner!), TRP730 (3.7 Å), and ASP729 (4.0 Å). The C733-C765 distance of 3.5 Å is consistent with a possible disulfide bond in the oxidizing ER lumen. The Atlas's C690R/C690Y cards discuss a similar C673-C690 inferred disulfide; C733-C765 may be a second analogous structural disulfide in the lumenal domain. Replacing C733 with glycine eliminates this potential disulfide entirely. The fold loses a major structural anchor. The |ΔΔG| of 1.15 reflects this — meaningful destabilization for a single substitution. AlphaMissense's 0.912 + Wolfram 1 clinical evidence confirm severe functional consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.912	**-1.15** kcal/mol	**88.50**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992006242	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	1/01/01 00:00
Inheritance	Wolfram syndrome 1 (AR) documented.
WFS1 variant landscape	C733G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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| = 1.15 — fold survives at meaningful cost. AlphaMissense 0.912 + Wolfram 1 confirm severe functional consequence.

Mechanism is loss of an inferred C733-C765 disulfide bond. Therapeutic strategy: site-directed at the C765 partner site, potentially with a small molecule that bridges the two former cysteines.

C733-C765 is the second possible disulfide pair identified in the Atlas (after C673-C690). The lumenal domain appears to use multiple structural disulfides; variants at any of these cysteines disrupt the fold.