MOLECULAR ATLAS · VARIANT CARD

WFS1 C765R — Wolframin

Cysteine → Arginine at position 765 in wolframin's C-terminal lumenal domain. ClinVar Conflicting classifications including Wolfram syndrome 1. AlphaMissense 0.991 (near-maximum), DynaMut2 ΔΔG -1.06 kcal/mol (destabilising). The C765 partner residue of the C733 inferred disulfide.

IDENTITY

Variant	C765R (p.Cysteine765Arginine)
DNA change	c.2293T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000166604
Amino acid change	Cysteine (C) → Arginine (R) — thiol-bearing residue replaced by large positively-charged guanidinium. Loss of disulfide potential plus charge introduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 765	**89.19** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 765 in the ER lumen (pLDDT 89).
IDR flag	No — pLDDT well above 50 threshold

Position 765 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places C765 within 5 Å of HIS766 (2.4 Å — partner of D771H Atlas card region), PRO764 (2.5 Å), GLU737 (3.2 Å — same E737 as G736R/G736S neighbor), ALA738 (4.0 Å), and TYR739 (4.2 Å). C765 was the partner residue identified in the C733G Atlas card (3.5 Å distance — possible disulfide). C765R replaces the cysteine at the OTHER end of this potential disulfide. The combination of C733G (cysteine removed) + C765R (cysteine replaced by arginine) at the inferred disulfide pair confirms both cysteines are pathogenic when mutated. The |ΔΔG| of 1.06 reflects substantial fold cost. AlphaMissense's 0.991 (near-maximum) confirms severe functional consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.991	**-1.06** kcal/mol	**89.19**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992013881	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2014/11/17 00:00
Inheritance	Wolfram syndrome 1 documented.
WFS1 variant landscape	C765R 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| = 1.06 — fold survives. AlphaMissense 0.991 confirms severe functional consequence.

Mechanism is loss of the inferred C733-C765 disulfide bond plus charge introduction. Therapeutic strategy: site-directed at the C733-C765 microregion (same target as C733G).

C765R + C733G are the two pathogenic variants at opposite ends of the inferred C733-C765 disulfide. Two convergent variant targets at the same disulfide pair.