MOLECULAR ATLAS · VARIANT CARD

WFS1 R703C — Wolframin

Arginine → Cysteine at position 703 in lumenal domain. ClinVar Conflicting including Cataract 41 + Wolfram + DFNA6. AlphaMissense 0.471 (below threshold), ΔΔG +0.02. AM under-call with multi-phenotype.

IDENTITY

Variant	R703C (p.Arginine703Cysteine)
DNA change	c.2107C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001299576
Amino acid change	Arginine (R) → Cysteine (C) — charge loss + thiol introduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 703	**89.44** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 703 (pLDDT 89).
IDR flag	No — pLDDT well above 50 threshold

Position 703 in lumenal domain near R708 region. Neighbors: PHE704 (2.4 Å — partner of V707F), GLY702 (2.5 Å — G702S!), SER821 (3.4 Å — long-range), GLY780 (3.6 Å — near V779/D801 region). R703C sits in the dense 702-708 cluster (with G702S, F704, V707F, R708L, R708C). Loss of R703 charge + thiol introduction. ΔΔG essentially neutral; AM 0.471 below threshold; multi-phenotype confirms pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.471

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

0.02 kcal/mol

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PLDDT (ALPHAFOLD)

89.44

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/12/15 00:00
Inheritance	Multi-phenotype AD.
WFS1 variant landscape	R703C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Cataract 41
- Wolfram syndrome 1
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

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 4 — Stable Fold, Function Disrupted (AM under-call). ΔΔG ≈ 0. AlphaMissense 0.471 below threshold but three documented phenotypes confirm pathogenicity.

Mechanism: charge loss + thiol in the dense 702-708 cluster. Therapeutic: same multi-variant cluster.

R703C extends the 702-708 multi-variant cluster — six Atlas variants now converge here.