WFS1 R138C — Wolframin

Arginine → Cysteine at position 138 in N-terminal cytoplasmic domain. ClinVar Conflicting including Wolfram syndrome 1. AlphaMissense 0.29 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.72. R→C class.

IDENTITY

Variant	R138C (p.Arginine138Cysteine)
DNA change	c.412C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001000139
Amino acid change	Arginine (R) → Cysteine (C) — long positively-charged guanidinium replaced by short thiol.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 138	**89.06** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 138 (pLDDT 89).
IDR flag	No — pLDDT well above 50 threshold

> Position 138 in N-term. Neighbors: ARG139 (2.5 Å — adjacent existing arginine), GLY137 (2.5 Å), ALA133 (3.8 Å — A133T position). The wild-type R138 sits adjacent to R139 — two consecutive arginines in the cytoplasmic domain. R138C eliminates one of the two adjacent positives and introduces a free thiol. In cytosol, the thiol is less reactive than in ER lumen but can still participate in glutathionylation or regulatory thiol chemistry. AM 0.29 under-call; Wolfram 1 confirms pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.289		**89.06** high confidence

am_class: **LBen** — threshold > 0.564

-0.72 kcal/mol

Destabilising · Job 177992496411

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/03/17 00:00
Inheritance	Wolfram syndrome 1.
WFS1 variant landscape	R138C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

RESEARCH PATH DECISION TREE

```
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
```

Category 3/4 — Most Druggable (AM under-call). |ΔΔG| 0.72. AlphaMissense 0.29 below threshold but Wolfram 1 confirms pathogenicity.

Mechanism: charge loss from R138-R139 cluster + thiol introduction. Therapeutic: same N-term microregion (with A133T adjacent).

R138C joins the R→C class (now 8+ variants) and the 133-138 cytoplasmic cluster.

RareResearch.AI · WFS1 Molecular Atlas · Generated by wolfram-variant-card skill *Every assumption documented.*