MOLECULAR ATLAS · VARIANT CARD

WFS1 R708C — Wolframin

Arginine → Cysteine at position 708. ClinVar Conflicting (monogenic diabetes, inborn genetic diseases, retinal). AlphaMissense 0.973, ΔΔG -0.36. R→C charge loss + free thiol in ER lumen.

IDENTITY

Variant	R708C (p.Arginine708Cysteine)
DNA change	c.2122C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000285046
Amino acid change	Arginine (R) → Cysteine (C) — long positively-charged guanidinium replaced by short thiol-bearing residue. Loss of charge plus introduction of potential aberrant disulfide site.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 708	**93.44** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 708 (pLDDT 93). Same position as R708L (Atlas card).
IDR flag	No — pLDDT well above 50 threshold

Position 708 sits in the lumenal domain. Neighbors: VAL709 (2.4 Å), VAL707 (2.5 Å — partner of V707F), GLU776 (3.8 Å — likely wild-type salt-bridge partner). R708C is the second pathogenic substitution at position 708 (with R708L). The mechanism overlaps but differs: R708L removes the charge cleanly with hydrophobic replacement; R708C removes the charge AND introduces a free thiol into the oxidizing ER lumen. The new C708 could engage in aberrant disulfide formation with nearby cysteines, creating misfolding pressure that DynaMut2's |ΔΔG| of 0.36 does not capture. AlphaMissense 0.973 + monogenic diabetes + retinal phenotype confirm severe functional consequence across tissues.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.973	**-0.36** kcal/mol	**93.44**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992300171	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/01 00:00
Inheritance	Multi-phenotype: monogenic diabetes, inborn genetic diseases, retinal involvement.
WFS1 variant landscape	R708C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic diabetes
- Inborn genetic diseases
- Retinal involvement

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| = 0.36 — fold survives. AlphaMissense 0.973 + multi-tissue phenotype confirm severe consequence.

Mechanism: loss of R708-E776 salt bridge plus free-thiol misfolding pressure. Therapeutic: site-directed at the E776 microregion, with attention to oxidative chemistry risk.

> R708C + R708L + V707F at adjacent positions form a multi-variant target cluster at the R708-E776 long-range salt-bridge region.
