MOLECULAR ATLAS · VARIANT CARD

WFS1 R818C — Wolframin

Arginine → Cysteine at position 818 in lumenal domain. ClinVar Conflicting including monogenic diabetes + WFS1 spectrum. AlphaMissense 0.38 (below threshold), DynaMut2 ΔΔG +0.24 kcal/mol (mild stabilising). Another R→C class variant with free-thiol risk.

IDENTITY

Variant	R818C (p.Arginine818Cysteine)
DNA change	c.2452C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000130748
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 818	**85.81** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 818 in the ER lumen (pLDDT 86).
IDR flag	No — pLDDT well above 50 threshold

Position 818 sits in wolframin's C-terminal lumenal domain. Neighbors: GLN819 (2.4 Å — same Q819 contacted by K705N/E across the fold!), LEU817 (2.5 Å), SER821 (4.4 Å — same S821 contacted by R703C across the fold). The Q819 and S821 contacts are structurally significant — R818 sits in a long-range contact network with the R705-Q819 microregion. Replacing R818 with cysteine eliminates the positive charge contributing to the Q819 contact and introduces a free thiol into the oxidizing ER lumen. The new C818 could engage in aberrant disulfide chemistry with nearby cysteines (no immediate cysteine partners within 5 Å, but the lumenal domain has multiple cysteines that could be reached). The ΔΔG of +0.24 is mild stabilising — the fold packs efficiently with the smaller cysteine. AlphaMissense's 0.38 is below threshold (AM under-call). Multi-phenotype

clinical evidence (monogenic diabetes + WFS1 spectrum) confirms pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.382	**0.24** kcal/mol	**85.81**
am_class: **Amb** — threshold > 0.564	Stabilising · Job 177992477338	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/02/01 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	R818C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic diabetes
- WFS1-Related Spectrum Disorders

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 +0.24 stabilising. AlphaMissense 0.38 below threshold but multi-phenotype clinical confirms pathogenicity.

Mechanism: loss of R818 charge from Q819-S821 long-range contact network + free-thiol introduction with aberrant disulfide risk. Therapeutic strategy: site-directed at the Q819 microregion (shared with K705N/E).

> R818C joins the growing R→C disulfide-risk class. The Q819 long-range contact links this variant to the K705 region — convergent multi-variant target.
