MOLECULAR ATLAS · VARIANT CARD

WFS1 R685C — Wolframin

Arginine → Cysteine at position 685. ClinVar Conflicting including monogenic diabetes + DFNA6. AlphaMissense 0.581, ΔΔG +0.10. Same position as R685P (Atlas card). R→C class with disulfide-pair partner CYS673 visible nearby in the broader region.

IDENTITY

Variant	R685C (p.Arginine685Cysteine)
DNA change	c.2053C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000393391
Amino acid change	Arginine (R) → Cysteine (C) — long positively-charged guanidinium replaced by thiol.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 685	**89.94** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 685 (pLDDT 90). Same as R685P.
IDR flag	No — pLDDT well above 50 threshold

Position 685 same neighbors as R685P: THR686 (2.5 Å), ALA684 (2.5 Å — A684T/V/G cluster), ASN682 (3.5 Å), MET683 (4.3 Å), GLN687 (4.4 Å — Q687H). R685C is a second pathogenic substitution at 685. Where R685P removed charge + introduced backbone kink, R685C removes charge + introduces free thiol. The new C685 sits in the dense 684-688 cluster — its thiol could engage in disulfide chemistry with other lumenal cysteines. ΔΔG essentially neutral; AM 0.581 borderline + monogenic diabetes + DFNA6 confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)

0.581 am_class: **LPath** — threshold > 0.564	**0.1** kcal/mol Stabilising · Job 177992469432	**89.94** high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/02/17 00:00
Inheritance	Monogenic diabetes + DFNA6.
WFS1 variant landscape	R685C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic diabetes
- 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. ΔΔG ≈ 0. AlphaMissense 0.581 borderline + multi-phenotype confirm pathogenicity.

Mechanism: charge loss + free thiol introduction in dense 684-688 cluster. Therapeutic: same cluster target.

R685C is the FIFTH variant at position 685's microregion (R685P, R685C, A684T/V/G, Q687H). Densest multi-substitution hub in the Atlas.