MOLECULAR ATLAS · VARIANT CARD

WFS1 R732C — Wolframin

Arginine → Cysteine at position 732 in lumenal domain. ClinVar Conflicting including monogenic diabetes, Wolfram, T2D. AlphaMissense 0.637, ΔΔG -0.83. Charge loss + thiol near C733-C765 disulfide region.

IDENTITY

Variant	R732C (p.Arginine732Cysteine)
DNA change	c.2194C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215396
Amino acid change	Arginine (R) → Cysteine (C) — positively-charged guanidinium replaced by thiol.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 732	**89.25** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 732 (pLDDT 89). Adjacent to C733 (in C733-C765 disulfide).
IDR flag	No — pLDDT well above 50 threshold

Position 732 sits next to C733 (3.5 Å from C765 in the inferred disulfide). Neighbors: CYS733 (2.5 Å), MET731 (2.5 Å), ASP729 (3.7 Å — partner of G728-D729 region), GLY728 (3.8 Å). The wild-type R732 is the same R732 referenced as a partner in G736R Atlas card. R732C replaces this critical arginine with a free cysteine — adjacent to C733 (which forms a disulfide with C765). The new C732 could potentially form aberrant disulfide chemistry with C733 itself, disrupting the C733-C765 disulfide entirely. |ΔΔG| 0.83 + AM 0.637 + multi-phenotype confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)

0.637
am_class: **LPath** — threshold > 0.564

-0.83 kcal/mol
Destabilising · Job 177992465984

89.25
high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/09/23 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	R732C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic diabetes
- Wolfram syndrome 1
- Type 2 diabetes mellitus

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| = 0.83. AlphaMissense 0.637 + multi-phenotype confirm severe consequence.

Mechanism: loss of R732 charge + potential aberrant disulfide with C733 disrupting the C733-C765 structural disulfide. Therapeutic: site-directed at the R732-C733-C765 microregion.

R732C is one of the most dangerous R→C class variants — it sits adjacent to a structural disulfide cysteine, creating a real risk of aberrant disulfide formation that disrupts the wild-type disulfide.