MOLECULAR ATLAS · VARIANT CARD

WFS1 R732H — Wolframin

Arginine → Histidine at position 732 in lumenal domain. ClinVar Conflicting including T2D. AlphaMissense 0.386 (below threshold), ΔΔG -0.94. Same position as R732C — second substitution at 732 in the C733-C765 disulfide region.

IDENTITY

Variant	R732H (p.Arginine732Histidine)
DNA change	c.2195G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215397
Amino acid change	Arginine (R) → Histidine (H) — long positively-charged amine replaced by small titratable aromatic. Charge reduced (pH-dependent).

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). Same as R732C.
IDR flag	No — pLDDT well above 50 threshold

Position 732 same neighbors as R732C: CYS733 (2.5 Å — C733-C765 disulfide cysteine), MET731 (2.5 Å), ASP729 (3.7 Å), GLY728 (3.8 Å). R732H is the second substitution at R732. Where R732C eliminated charge + introduced thiol, R732H reduces charge to pH-dependent. The C733 disulfide partner is less perturbed than in R732C (no new aberrant thiol). |ΔΔG| 0.94 + AM 0.386 under-call + T2D confirm pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.386		89.25

am_class: **Amb** — threshold > 0.564

-0.94 kcal/mol

Destabilising · Job 177992474817

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/15 00:00
Inheritance	T2D documented.
WFS1 variant landscape	R732H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- 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 (AM under-call). |ΔΔG| 0.94. AlphaMissense 0.386 below threshold but T2D confirms pathogenicity.

Mechanism: partial charge loss + perturbation of C733 disulfide region from adjacent position. Therapeutic: same C733-C765 microregion as R732C, C733G, C765R, L734H.

R732H joins R732C at position 732 — both at the C733 disulfide-adjacent position. Five Atlas variants now converge on the 732-734 microregion.