MOLECULAR ATLAS · VARIANT CARD

WFS1 R457S — Wolframin

Arginine → Serine at position 457 in connecting loop. ClinVar Conflicting including monogenic diabetes + spastic. AlphaMissense 0.515 (borderline), ΔΔG -0.82.

IDENTITY

Variant	R457S (p.Arginine457Serine)
DNA change	c.1371G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215389
Amino acid change	Arginine (R) → Serine (S) — long positively-charged amine replaced by small polar hydroxyl. Loss of charge + side-chain length.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 457	**88.25** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 457 (pLDDT 88).
IDR flag	No — pLDDT well above 50 threshold

> Position 457 in connecting loop. Neighbors: ALA458 (2.5 Å), ARG456 (2.5 Å — adjacent existing arginine!), TYR454 (3.7 Å), PRO453 (4.1 Å). Replacing R457 with serine eliminates one of two adjacent arginines (R456 + R457). The local positively-charged surface character is reduced. ΔΔG 0.82 + AM 0.515 borderline + monogenic diabetes confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.515	**-0.82** kcal/mol	**88.25**
am_class: **Amb** — threshold > 0.564	Destabilising · Job 177992469629	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/11/18 00:00
Inheritance	Monogenic diabetes + WFS1 spectrum.
WFS1 variant landscape	R457S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-related disorder
- Monogenic diabetes
- Spastic ataxia

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| = 0.82. AlphaMissense 0.515 borderline + multi-phenotype confirm severe consequence.

Mechanism: loss of R457 charge from R456-R457 cluster. Therapeutic: site-directed at the loop's charged surface.

R457S continues the charge-loss class in connecting loops.

RareResearch.AI · WFS1 Molecular Atlas · Generated by wolfram-variant-card skill *Every assumption documented.*