MOLECULAR ATLAS · VARIANT CARD

WFS1 R456H — Wolframin

Arginine → Histidine at position 456 in connecting loop. ClinVar Conflicting including WFS1 spectrum. AlphaMissense 0.16 (below threshold) — AM under-call. DynaMut2 ΔΔG -1.26 (substantial). Adjacent to R457S.

IDENTITY

Variant	R456H (p.Arginine456Histidine)
DNA change	c.1367G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000045434
Amino acid change	Arginine (R) → Histidine (H) — charge partial-reduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 456	**85.69** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 456 (pLDDT 86).
IDR flag	No — pLDDT well above 50 threshold

Position 456 in connecting loop. Neighbors: ARG457 (2.5 Å — R457S partner!), THR455 (2.5 Å), GLU452 (3.6 Å — likely salt-bridge). R456H + R457S both at the R456-R457 double-arginine cluster. Partial charge reduction + perturbed E452 salt bridge. |ΔΔG| 1.26 substantial; AM 0.16 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.159

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-1.26 kcal/mol

Destabilising · Job 177992502783

PLDDT (ALPHAFOLD)

85.69

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/02/03 00:00
Inheritance	WFS1 spectrum.
WFS1 variant landscape	R456H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- 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 3/4 — Most Druggable (AM under-call). |ΔΔG| 1.26. AlphaMissense 0.16 below threshold but multi-phenotype + substantial ΔΔG confirm pathogenicity.

Mechanism: partial charge loss from R456-R457 cluster + E452 salt-bridge disruption. Therapeutic: same loop as R457S.

R456H + R457S — adjacent variants in 456-457 charged cluster.