MOLECULAR ATLAS · VARIANT CARD

WFS1 R228H — Wolframin

Arginine → Histidine at position 228 in N-terminal cytoplasmic domain. ClinVar Conflicting including WFS1 spectrum + Wolfram. AlphaMissense 0.20 (below threshold) — AM under-call. DynaMut2 ΔΔG -1.17 (substantial destabilising).

IDENTITY

Variant	R228H (p.Arginine228Histidine)
DNA change	c.683G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000198190
Amino acid change	Arginine (R) → Histidine (H) — long positively-charged amine replaced by smaller titratable basic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 228	**76.00** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 228 (pLDDT 76).
IDR flag	No — pLDDT well above 50 threshold

Position 228 in cytoplasmic domain. Neighbors: MET229 (2.5 Å), ARG227 (2.5 Å — adjacent existing arginine!), GLU231 (3.5 Å — likely salt-bridge partner). The R227-R228 double-arginine plus E231 forms a charged surface patch. R228H reduces charge to pH-dependent. The R227 + H228 pair has different electrostatic character than R227 + R228. |ΔΔG| 1.17 substantial; AM 0.20 under-call; multi-phenotype confirms pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.196

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

PLDDT (ALPHAFOLD)

76.00

high confidence

-1.17 kcal/mol

Destabilising · Job 177992498491

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/26 00:00
Inheritance	WFS1 spectrum.
WFS1 variant landscape	R228H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-Related Spectrum Disorders
- Wolfram syndrome 1

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| 1.17 substantial. AlphaMissense 0.20 below threshold but multi-phenotype + substantial ΔΔG confirm pathogenicity.

Mechanism: charge partial-loss from R227-R228-E231 cluster. Therapeutic: cytoplasmic recognition surface site-directed.

R228H continues charge-cluster-loss class in cytoplasmic domain.