MOLECULAR ATLAS · VARIANT CARD

WFS1 R146C — Wolframin

Arginine → Cysteine at position 146 in N-terminal cytoplasmic domain. ClinVar Conflicting including Wolfram syndrome 1. AlphaMissense 0.19 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.38. R→C class.

IDENTITY

Variant	R146C (p.Arginine146Cysteine)
DNA change	c.436C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000517251
Amino acid change	Arginine (R) → Cysteine (C) — charge loss + thiol introduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 146	**92.31** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 146 (pLDDT 92).
IDR flag	No — pLDDT well above 50 threshold

Position 146 in cytoplasmic domain. Neighbors: ARG147 (2.4 Å — adjacent existing arginine), LEU145 (2.5 Å), LYS143 (3.8 Å). R146-R147 adjacent positives + K143 nearby — positively-charged surface patch. R146C eliminates one of the cluster's positives + introduces thiol. AM 0.19 under-call; Wolfram 1 confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.195

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.38 kcal/mol

Destabilising · Job 177992498999

PLDDT (ALPHAFOLD)

92.31

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2017/02/16 00:00
Inheritance	Wolfram syndrome 1.
WFS1 variant landscape	R146C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- 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| 0.38. AlphaMissense 0.19 below threshold but Wolfram 1 confirms.

Mechanism: charge loss from R146-R147-K143 cluster. Therapeutic: site-directed at cytoplasmic recognition surface.

R146C continues R→C class (now 9+ variants).