MOLECULAR ATLAS · VARIANT CARD

WFS1 R676H — Wolframin

Arginine → Histidine at position 676 in lumenal domain. ClinVar Conflicting including DFNA6. AlphaMissense 0.12 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.54.

IDENTITY

Variant	R676H (p.Arginine676Histidine)
DNA change	c.2027G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000426907
Amino acid change	Arginine (R) → Histidine (H) — charge partial-reduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 676	**81.12** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 676 (pLDDT 81).
IDR flag	No — pLDDT well above 50 threshold

Position 676 in lumenal domain. Neighbors: ALA677 (2.5 Å), PRO675 (2.5 Å — adjacent to G674 cluster!), GLY674 (4.0 Å — G674 multi-variant position!). R676H sits in the dense G674 cluster region. |ΔΔG| 0.54; AM 0.12 under-call; DFNA6 confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.122

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.54 kcal/mol

Destabilising · Job 177992508941

PLDDT (ALPHAFOLD)

81.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/09/07 00:00
Inheritance	DFNA6.
WFS1 variant landscape	R676H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

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| 0.54. AlphaMissense 0.12 below threshold but DFNA6 confirms.

Mechanism: partial charge loss adjacent to G674 cluster. Therapeutic: same G674-R676 microregion.

R676H extends the G674 cluster region — now 5+ variants converge on position 674 ± neighbors.