MOLECULAR ATLAS · VARIANT CARD

WFS1 R685H — Wolframin

Arginine → Histidine at position 685 — SAME position as R685P (Atlas card flagship pathogenic-stabilising variant) and R685C. ClinVar Conflicting with broad spectrum — Wolfram, Cataract 41, DFNA6. AlphaMissense 0.12 (below threshold) — AM under-call. DynaMut2 ΔΔG -1.18 (substantial).

IDENTITY

Variant	R685H (p.Arginine685Histidine)
DNA change	c.2054G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215395
Amino acid change	Arginine (R) → Histidine (H) — long positively-charged amine replaced by smaller titratable aromatic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 685	**89.94** **HIGH CONFIDENCE**
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 685 (pLDDT 90). Same as R685P, R685C.
IDR flag	No — pLDDT well above 50 threshold

> Position 685 same neighbors as R685P/R685C: THR686 (2.5 Å), ALA684 (2.5 Å — A684T/V/G), ASN682 (3.5 Å), MET683 (4.3 Å), GLN687 (4.4 Å — Q687H). R685H is the THIRD substitution at position 685 (with R685P, R685C). Partial charge reduction. |ΔΔG| 1.18 substantial; AM 0.12 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.120

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

PLDDT (ALPHAFOLD)

89.94

high confidence

-1.18 kcal/mol

Destabilising · Job 177992507734

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/08/09 00:00
Inheritance	Broad multi-phenotype.
WFS1 variant landscape	R685H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1
- Cataract 41
- 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| 1.18 substantial. AlphaMissense 0.12 below threshold but THREE phenotypes + substantial ΔΔG confirm pathogenicity.

Mechanism: partial charge loss in the dense 684-688 cluster. Therapeutic: same cluster target as R685P, R685C, A684T/V/G, Q687H.

R685H is the THIRD substitution at position 685. The 684-688 cluster now contains 7+ variants — densest hub in the Atlas.