MOLECULAR ATLAS · VARIANT CARD

WFS1 R703H — Wolframin

Arg→His p703 lumenal AM=0.10 ddg=-1.21 pLDDT=89. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	R703H (p.Arginine703Histidine)
DNA change	c.2108G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001297606
Amino acid change	partial charge reduction

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 703	**89.44** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: PHE704 (2.4 Å), GLY702 (2.5 Å — G702S!), SER821 (3.4 Å — long-range). Substantial ΔΔG. Same dense 702-708 cluster. The Atlas's neighbor extraction surfaces this variant's contacts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.104

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-1.21 kcal/mol

Destabilising · Job 177992512348

PLDDT (ALPHAFOLD)

89.44

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/03/19 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	R703H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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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Cat 3/4 — see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally clear from neighbor analysis. Therapeutic strategy: site-directed at the contacts identified above.

Continues 702-708 dense cluster.
