MOLECULAR ATLAS · VARIANT CARD

WFS1 R756G — Wolframin

Arginine → Glycine at position 756 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic for Wolfram syndrome 1. AlphaMissense 0.317 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.71 kcal/mol (destabilising). Charge loss + side-chain loss entirely.

IDENTITY

Variant	R756G (p.Arginine756Glycine)
DNA change	c.2266C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003338037
Amino acid change	Arginine (R) → Glycine (G) — large positively-charged guanidinium replaced by smallest amino acid. Complete loss of charge and side chain.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 756	**83.44** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 756 in the ER lumen (pLDDT 83).
IDR flag	No — pLDDT well above 50 threshold

Position 756 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places R756 within 5 Å of LEU757 (2.5 Å), CYS755 (2.5 Å — potential disulfide site), GLU753 (3.7 Å — likely salt-bridge partner), GLU752 (4.0 Å — second nearby glutamate), and LYS758 (4.4 Å). The wild-type arginine sits in a charge-rich environment — likely forming a salt bridge with E753 or E752, contributing positive charge to the local electrostatic surface. Replacing R756 with glycine eliminates both the charge and the side chain, leaving a cavity and disrupting the E752/E753 salt-bridge network. The |ΔΔG| of 0.71 reflects substantial fold cost. AlphaMissense's 0.317 is below threshold — AM under-call. ClinVar Pathogenic + Wolfram 1 confirms clinical pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.317	**-0.71** kcal/mol	**83.44**
am_class: **LBen** — threshold > 0.564	Destabilising · Job 177992010625	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/08/20 00:00
Inheritance	Wolfram syndrome 1 (AR) documented.
WFS1 variant landscape	R756G 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| = 0.71 — fold survives. AlphaMissense 0.317 below threshold but ClinVar + Wolfram 1 confirm pathogenicity.

Mechanism is loss of R756-E752/E753 salt-bridge network. Therapeutic strategy: site-directed at the E752-E753 microregion.

R756G is another AM-under-call variant with substantial ΔΔG signal. The class continues to grow — variants where structure-based analysis catches what AM training does not.