MOLECULAR ATLAS · VARIANT CARD

WFS1 R868H — Wolframin

Arginine → Histidine at position 868 near the lumenal C-terminus. ClinVar Conflicting including WFS1 spectrum. AlphaMissense 0.19 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.72. pLDDT 68 borderline.

IDENTITY

Variant	R868H (p.Arginine868Histidine)
DNA change	c.2603G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215403
Amino acid change	Arginine (R) → Histidine (H) — charge partial-reduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 868	**67.62** CONFIDENT
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 868 (pLDDT 68 borderline).
IDR flag	No — pLDDT well above 50 threshold

Position 868 near C-terminus. Neighbors: SER869 (2.5 Å), TRP867 (2.5 Å — W867 in TM11 cluster), ASP866 (4.0 Å — D866N region). R868H sits in the dense 866-876 C-terminal microregion (with D866N, K876T, K862N, E864K). Partial charge loss + perturbed D866 salt-bridge contact. AM 0.19 under-call; multi-phenotype confirms pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.191

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.72 kcal/mol

Destabilising · Job 177992498658

PLDDT (ALPHAFOLD)

67.62

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/12/10 00:00
Inheritance	WFS1 spectrum.
WFS1 variant landscape	R868H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Inborn genetic diseases
- WFS1-Related Spectrum Disorders

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| 0.72. AlphaMissense 0.19 below threshold but multi-phenotype confirms pathogenicity.

Mechanism: partial charge loss in C-terminal multi-variant cluster. Therapeutic: same 866-876 microregion as D866N, K862N, E864K, K876T.

R868H extends C-terminal cluster — now 6+ variants converging.