MOLECULAR ATLAS · VARIANT CARD

WFS1 R859Q — Wolframin

Arginine → Glutamine at position 859 in lumenal C-terminal region. ClinVar Conflicting including optic atrophy + DFNA6. AlphaMissense 0.11 (below threshold) — AM under-call. DynaMut2 ΔΔG +0.22. pLDDT 56 borderline.

IDENTITY

Variant	R859Q (p.Arginine859Glutamine)
DNA change	c.2576G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000004529
Amino acid change	Arginine (R) → Glutamine (Q) — long positively-charged amine replaced by neutral polar amide.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 859	**55.84** CONFIDENT
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 859 (pLDDT 56 borderline).
IDR flag	No — pLDDT well above 50 threshold

> Position 859 in lumenal C-terminus. Neighbors: HIS860 (2.4 Å), ARG858 (2.5 Å — adjacent existing arginine), THR857 (4.1 Å). R859Q charge loss in R858-R859 adjacent arginine cluster. AM 0.11 under-call; optic atrophy + DFNA6 confirm.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.106

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.22 kcal/mol

Stabilising · Job 177992509798

PLDDT (ALPHAFOLD)

55.84

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/02/01 00:00
Inheritance	Multi-phenotype AD.
WFS1 variant landscape	R859Q is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-related disorder
- Optic atrophy
- 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 4 — Stable Fold, Function Disrupted (AM under-call, pLDDT borderline). ΔΔG +0.22. AlphaMissense 0.11 below threshold but optic atrophy + DFNA6 confirm.

Mechanism: charge loss from R858-R859 cluster. Therapeutic: C-terminal microregion.

R859Q joins the C-terminal cluster — connecting the K843-V861 region with 859-868.
