MOLECULAR ATLAS · VARIANT CARD

WFS1 R818H — Wolframin

Arg→His p818 lumenal AM=0.11 ddg=-0.17 pLDDT=86. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	R818H (p.Arginine818Histidine)
DNA change	c.2453G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215414
Amino acid change	partial charge reduction

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 818	**85.81** 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: GLN819 (2.4 Å), LEU817 (2.5 Å), SER821 (4.4 Å). Same Q819 long-range contact as R818C, K705N. Multi-variant convergence. The Atlas's neighbor extraction surfaces this variant's contacts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.109

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.17 kcal/mol

Destabilising · Job 177992512014

PLDDT (ALPHAFOLD)

85.81

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/12/18 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	R818H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

RESEARCH PATH DECISION TREE

```
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
```

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.

Same Q819 hub as R818C, K705 region.
