MOLECULAR ATLAS · VARIANT CARD

WFS1 K811R — Wolframin

Lys→Arg p811 lumenal AM=0.07 ddg=-0.28 pLDDT=86. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	K811R (p.Lysine811Arginine)
DNA change	c.2432A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001160733
Amino acid change	conservative basic-to-basic

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 811	**86.25** 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: SER812 (2.5 Å), PHE810 (2.5 Å — F810L partner!), SER808 (3.8 Å — E809K region). Same E809-F810-K811 cluster as E809K/F810L. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.073

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.28 kcal/mol

Destabilising · Job 177992523974

PLDDT (ALPHAFOLD)

86.25

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/05/21 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	K811R 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 4 — see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally identified. Therapeutic strategy: site-directed at contacts identified above, or wet-lab validation if pLDDT borderline/below 50.

E809K + F810L + K811R cluster.
