MOLECULAR ATLAS · VARIANT CARD

WFS1 E794K — Wolframin

Glutamate → Lysine at position 794 in lumenal domain. ClinVar Conflicting including Wolfram syndrome 1. AlphaMissense 0.24 (below threshold) — AM under-call. DynaMut2 ΔΔG +0.49 STABILISING. pLDDT 49 — Category 5 IDR boundary!

IDENTITY

Variant	E794K (p.Glutamate794Lysine)
DNA change	c.2380G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000198836
Amino acid change	Glutamate (E) → Lysine (K) — charge reversal.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 794	**49.00** BELOW IDR THRESHOLD
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 794 (pLDDT 49 — IDR boundary).
IDR flag	YES — pLDDT 49.00 is below 50 threshold (route to Cat 5)

> Position 794 at pLDDT 49 — RIGHT AT the Category 5 IDR threshold. Computational predictions deserve caution. Neighbors: GLU795 (2.5 Å), ARG793 (2.5 Å), SER792 (3.8 Å). E794K charge-flips in a borderline IDR region. ΔΔG predictions not trustworthy here. AM 0.24 below threshold but Wolfram 1 documented.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.242

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.49 kcal/mol

Stabilising · Job 177992498005

PLDDT (ALPHAFOLD)

49.00

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/26 00:00
Inheritance	Wolfram syndrome 1.
WFS1 variant landscape	E794K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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
```

Category 5 — IDR Exclusion (borderline). pLDDT 49 at the 50 threshold. AlphaMissense 0.24 below threshold. Multiple signals suggest computational caution.

The Atlas routes Category 5 variants to wet-lab characterization rather than computational drug discovery.

E794K is another borderline IDR variant — Atlas appropriately flags for wet-lab work.