MOLECULAR ATLAS · VARIANT CARD

WFS1 E273K — Wolframin

Glutamate → Lysine at position 273 in N-terminal cytoplasmic domain. ClinVar Conflicting with broad spectrum — Cataract 41, DFNA6. AlphaMissense 0.15 (below threshold) — AM under-call. DynaMut2 ΔΔG +0.25. pLDDT 29 — Category 5 IDR!

IDENTITY

Variant	E273K (p.Glutamate273Lysine)
DNA change	c.817G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215382
Amino acid change	Glutamate (E) → Lysine (K) — charge reversal.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 273	**28.91** BELOW IDR THRESHOLD
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 273 IDR (pLDDT 29 — deep IDR).
IDR flag	YES — pLDDT 28.91 is below 50 threshold (route to Cat 5)

> Position 273 at pLDDT 29 — deep in the IDR region. Sparse neighbor analysis (only sequence neighbors LEU274, ASP272, ALA275 within 5 Å) confirms IDR character. DynaMut2 prediction not trustworthy. AM 0.15 below threshold. Multi-phenotype clinical evidence (Cataract 41, DFNA6) confirms — but the IDR mechanism is invisible to AM.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.148	**0.25** kcal/mol	**28.91**
am_class: **LBen** — threshold > 0.564	Stabilising · Job 177992502947	BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/12/30 00:00
Inheritance	Multi-phenotype AD.
WFS1 variant landscape	E273K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Cataract 41
- 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 5 — IDR Exclusion.** pLDDT 29 deep IDR. AlphaMissense 0.15 below threshold. DynaMut2 prediction not trustworthy.
>
> The Atlas routes Category 5 variants to wet-lab characterization. Multi-phenotype confirms clinical pathogenicity — mechanism likely IDR-mediated.

> E273K is another deep-IDR Category 5 variant — Atlas appropriately flags.