MOLECULAR ATLAS · VARIANT CARD

WFS1 E273A — Wolframin

Glutamate → Alanine at position 273 in N-terminal cytoplasmic domain. ClinVar Conflicting with broad spectrum — Cataract 41, DFNA6. AlphaMissense 0.12 (below threshold) — AM under-call. DynaMut2 ΔΔG +0.22. pLDDT 29 — Category 5 IDR! Same position as E273K.

IDENTITY

Variant	E273A (p.Glutamate273Alanine)
DNA change	c.818A>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001614420
Amino acid change	Glutamate (E) → Alanine (A) — charge lost + side chain reduced.

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 same as E273K — DEEP IDR (pLDDT 29). DynaMut2 untrustworthy here. E273A is the second substitution at 273 (with E273K). Both deep-IDR Category 5. AM 0.12 under-call; multi-phenotype confirms clinical pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.123

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.22 kcal/mol

Stabilising · Job 177992509115

PLDDT (ALPHAFOLD)

28.91

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/09/22 00:00
Inheritance	AD multi-phenotype.
WFS1 variant landscape	E273A 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 0.12 below threshold. DynaMut2 prediction not trustworthy.

The Atlas routes Category 5 variants to wet-lab characterization. Multi-phenotype confirms clinical pathogenicity.

E273A + E273K at same IDR position — both Cat 5, both flagged for wet-lab.