MOLECULAR ATLAS · VARIANT CARD

WFS1 E158K — Wolframin

Glutamate → Lysine at position 158 in N-terminal cytoplasmic domain. ClinVar Conflicting including Wolfram syndrome 1 + Cataract 41. AlphaMissense 0.378 (below threshold), ΔΔG +0.55 STABILISING.

IDENTITY

Variant	E158K (p.Glutamate158Lysine)
DNA change	c.472G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001404588
Amino acid change	Glutamate (E) → Lysine (K) — charge reversal.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 158	**86.62** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 158 (pLDDT 87).
IDR flag	No — pLDDT well above 50 threshold

> Position 158 in cytoplasmic domain. Neighbors: ASN159 (2.5 Å), SER157 (2.5 Å), THR156 (4.0 Å), GLU160 (4.6 Å — second nearby glutamate). E158K reverses charge. The E158-E160 charged pair becomes K158-E160 alternating charges. Fold stabilises slightly. AM 0.378 under-call; Wolfram + Cataract confirm pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.378

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

0.55 kcal/mol

Stabilising · Job 177992477506

PLDDT (ALPHAFOLD)

86.62

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/05/02 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	E158K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1
- Cataract 41

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 4 — Stable Fold, Function Disrupted (AM under-call, stabilising). ΔΔG +0.55. AlphaMissense 0.378 below threshold but multi-phenotype confirms.

Mechanism: charge-flip in E158-E160 pair. Therapeutic: cytoplasmic recognition surface.

E158K joins charge-flip class + AM-under-call class. Cytoplasmic recognition-surface disruption.
