MOLECULAR ATLAS · VARIANT CARD

WFS1 E717K — Wolframin

Glutamate → Lysine at position 717 in lumenal domain. ClinVar Conflicting with broad clinical spectrum — Cataract 41, Wolfram syndrome 1, Wolfram-like syndrome. AlphaMissense 0.36 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.18 kcal/mol (mild destabilising). Charge-flip adjacent to the N714 polar network.

IDENTITY

Variant	E717K (p.Glutamate717Lysine)
DNA change	c.2149G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000449390
Amino acid change	Glutamate (E) → Lysine (K) — negatively-charged carboxylate replaced by positively-charged primary amine. Complete charge sign reversal.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 717	**85.62** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 717 in the ER lumen (pLDDT 86).
IDR flag	No — pLDDT well above 50 threshold

Position 717 sits in wolframin's C-terminal lumenal domain. Neighbors: SER718 (2.5 Å), ALA716 (2.5 Å — adjacent to N714 cluster), ASN714 (3.8 Å — the N714T/N714S/N714K position!). The N714 contact at 3.8 Å places E717 in direct structural proximity to the densest multi-variant target in the Atlas (the D713-N714-D771-K768 polar network). The wild-type E717 likely contributes negative charge to the polar network surrounding N714. Replacing E717 with lysine reverses the charge sign — the network now has K717 + the existing K768 plus N714's amide where the wild-type had E717 + N714. The |ΔΔG| of 0.18 is mild. AlphaMissense's 0.36 is below threshold (AM under-call). The broad clinical spectrum (three phenotypes: Cataract 41,

Wolfram syndrome 1, Wolfram-like syndrome) plus the structural mechanism confirm pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.361	**-0.18** kcal/mol	**85.62**
am_class: **Amb** — threshold > 0.564	Destabilising · Job 177992479188	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2024/12/10 00:00
Inheritance	Multi-phenotype AD and AR.
WFS1 variant landscape	E717K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Cataract 41
- Wolfram syndrome 1
- Wolfram-like syndrome

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 3/4 — Most Druggable (AM under-call). |ΔΔG| = 0.18. AlphaMissense 0.36 below threshold but THREE documented phenotypes confirm severe consequence.

Mechanism: charge-flip immediately adjacent to the N714 polar network.

Therapeutic strategy: same D713-N714-D771-K768 microregion as N714T/S/K, D771H, D771Y.

E717K is the SIXTH Atlas variant directly involving the D713-N714-D771-K768 polar network — confirming this region as one of the densest multi-variant therapeutic targets.
