MOLECULAR ATLAS · VARIANT CARD

WFS1 E169K — Wolframin

Glutamate → Lysine at position 169 in wolframin's N-terminal cytoplasmic domain. ClinVar Pathogenic/Likely pathogenic across both AD and AR WFS1-related disorders. AlphaMissense 0.948, DynaMut2 ΔΔG -0.39 kcal/mol (destabilising). A clean charge-flip variant with documented dual-inheritance impact.

IDENTITY

Variant	E169K (p.Glutamate169Lysine)
DNA change	c.505G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215376
Amino acid change	Glutamate (E) → Lysine (K) — a negatively-charged carboxylate-bearing residue replaced by a positively-charged primary amine-bearing residue. The charge sign reverses completely; volume is roughly comparable.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 169	**86.50** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 169 sits in the cytosol-facing region with good AlphaFold confidence (pLDDT 86). The cytosolic environment accommodates charged side chains but the specific charge sign matters for partner interactions.
IDR flag	No — pLDDT well above 50 threshold

Position 169 sits in wolframin's N-terminal cytoplasmic domain. The AlphaFold model places E169 within 5 Å of THR170 (2.4 Å), SER168 (2.5 Å), GLU173 (3.9 Å), LEU166 (4.2 Å), and GLN165 (4.2 Å). The local environment is polar-leaning, with a nearby second glutamate (E173) suggesting the wild-type E169 may contribute to a charged surface patch. Replacing glutamate with lysine here reverses the charge sign at this position. Where the wild-type contributed a negative charge to the local electrostatic environment, the mutant contributes a positive one. The two glutamate residues E169 and

E173 may have been forming a negatively-charged cytoplasmic surface patch — a recognition signature for a partner protein with a complementary positively-charged surface. Flipping E169 to lysine destroys that recognition surface and replaces it with one of opposite character. The |ΔΔG| of 0.39 kcal/mol is modest because the fold itself accommodates the charge-flip — both glutamate and lysine are flexible polar residues. The structural cost is minor. But the functional cost — disrupted electrostatic recognition surface for partner proteins — is severe, captured by AlphaMissense's 0.948 score and the documented dual-inheritance clinical impact.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.948

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.39 kcal/mol

Destabilising · Job 177991404002

PLDDT (ALPHAFOLD)

86.50

high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/11/18 00:00
Inheritance	Both autosomal dominant and autosomal recessive WFS1-related disorders documented — a relatively rare profile that reflects the variant's mechanism affecting partner interactions in multiple cellular contexts.
WFS1 variant landscape	E169K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Autosomal dominant and autosomal recessive WFS1-related disorders
- 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 —
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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. |ΔΔG| = 0.39 kcal/mol — fold survives. AlphaMissense 0.948 + dual-inheritance clinical impact confirm severe functional consequence.

The mechanism is charge-sign reversal at a cytoplasmic recognition surface. The lost negative charge plus the new positive charge together disrupt whatever partner-protein recognition the wild-type E169/E173 patch enabled.

Therapeutic strategy: this is a functional-site disruption rather than a fold problem. Site-directed small-molecule design at the recognition surface — restoring or compensating for the lost negatively-charged patch — is the rational vector. Alternatively, if the disrupted recognition target can be identified, indirect rescue via the partner protein.

E169K is one of the few Atlas variants with the unusual dual-inheritance ClinVar classification, suggesting the disrupted partner interaction operates in multiple cellular contexts (with different consequences in homozygous, compound heterozygous, and heterozygous settings). The charge-flip mechanism class — where the substitution reverses charge sign without changing volume much — is structurally invisible to ΔΔG analysis but clear to AlphaMissense and clinical evidence.
