MOLECULAR ATLAS · VARIANT CARD

WFS1 K252E — Wolframin

Lysine → Glutamate at position 252 in N-terminal cytoplasmic domain. ClinVar Conflicting including Wolfram syndrome 1. AlphaMissense 0.872, ΔΔG -1.26. Charge-flip variant in cytoplasmic domain.

IDENTITY

Variant	K252E (p.Lysine252Glutamate)
DNA change	c.754A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000505263
Amino acid change	Lysine (K) → Glutamate (E) — positively-charged amine replaced by negatively-charged carboxylate. Complete charge reversal.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 252	**87.31** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 252 (pLDDT 87).
IDR flag	No — pLDDT well above 50 threshold

Position 252 sits in cytoplasmic domain. Neighbors: LYS253 (2.5 Å — adjacent existing lysine!), THR251 (2.5 Å), GLU249 (3.7 Å — likely salt-bridge partner with wild-type K252), VAL248 (3.7 Å). Replacing K252 with glutamate creates two negative charges (new E252 + existing E249) where wild-type had a positive K252 + negative E249 salt bridge. The local electrostatic surface flips polarity. |ΔΔG| 1.26 reflects substantial cost. AlphaMissense 0.872 + Wolfram 1 confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.872		**87.31**

am_class: **LPath** — threshold > 0.564

-1.26 kcal/mol

Destabilising · Job 177992463158

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2016/09/11 00:00
Inheritance	Wolfram syndrome 1.
WFS1 variant landscape	K252E is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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. |ΔΔG| = 1.26 — fold survives at meaningful cost. AlphaMissense 0.872 + Wolfram 1 confirm severe consequence.

Mechanism: charge-flip disrupting K252-E249 salt bridge + creating two-glutamate cluster. Therapeutic: site-directed at the 249-253 microregion.

K252E continues the charge-flip class (with E169K, E809K, E864K, K705E). Recognition-surface disruption through charge sign reversal.