MOLECULAR ATLAS · VARIANT CARD

WFS1 K705E — Wolframin

Lysine → Glutamate at position 705 in wolframin's C-terminal lumenal domain. ClinVar Conflicting classifications including Cataract 41. AlphaMissense 0.975, DynaMut2 ΔΔG -0.17 kcal/mol (mild destabilising). Charge-flip variant at the SAME position as K705N (Atlas card adjacent).

IDENTITY

Variant	K705E (p.Lysine705Glutamate)
DNA change	c.2113A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001685475
Amino acid change	Lysine (K) → Glutamate (E) — large positively-charged amine replaced by small negatively-charged carboxylate. Complete charge sign reversal.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 705	**90.00** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 705 in the ER lumen (pLDDT 90). Same position as K705N.
IDR flag	No — pLDDT well above 50 threshold

> Position 705 same neighbor environment as K705N: TYR706 (2.4 Å), PHE704 (2.5 Å), THR778 (3.6 Å), GLN819 (4.4 Å), ARG703 (4.5 Å). K705E is the charge-flip variant complementing K705N (charge-neutral) at this position. Where the wild-type K705 made a long-range contact (likely cation-π or salt bridge) with residues across the fold, the variant E705 makes opposite-sign electrostatic contacts. The R703 neighbor at 4.5 Å — previously experiencing K705's same-sign positive charge — now experiences an opposite-sign attractive contact. The |ΔΔG| of 0.17 is mild — fold accommodates the charge flip easily. AlphaMissense's 0.975 + Cataract 41 clinical evidence confirm severe functional consequence. The mechanism is charge-reversal at the long-range contact position that K705 supplied positive charge to.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.975

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.17 kcal/mol

Destabilising · Job 177992299337

PLDDT (ALPHAFOLD)

90.00

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2024/02/26 00:00
Inheritance	Cataract 41 documented.
WFS1 variant landscape	K705E is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- 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 3/4 — Most Druggable. |ΔΔG| = 0.17 — fold survives. AlphaMissense 0.975 + Cataract 41 confirm severe functional consequence.

Mechanism is charge-flip at K705 disrupting long-range contacts (THR778, GLN819). Therapeutic strategy: same microregion as K705N.

K705E + K705N at the same position with different chemistry — both pathogenic. The K705 position is structurally critical regardless of which residue substitutes.