MOLECULAR ATLAS · VARIANT CARD

WFS1 E385K — Wolframin

Glutamate → Lysine at position 385 in a connecting loop. ClinVar Conflicting including WFS1-Related Spectrum Disorders, monogenic diabetes. AlphaMissense 0.851, ΔΔG -0.16.

IDENTITY

Variant	E385K (p.Glutamate385Lysine)
DNA change	c.1153G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000178590
Amino acid change	Glutamate (E) → Lysine (K) — charge reversal.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 385	**85.44** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 385 (pLDDT 85).
IDR flag	No — pLDDT well above 50 threshold

Position 385 sits in a connecting loop. Neighbors: PHE384 (2.5 Å), PRO386 (2.5 Å), LEU381 (3.8 Å), LEU382 (4.2 Å — partner of L382P!). Adjacent to L382P region. E385K charge-flips at this position. The variant lysine likely engages different partners than the wild-type glutamate. Combined with L382P, multiple Atlas variants converge on the 381-386 loop. ΔΔG mild; AM 0.851 + multi-phenotype confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.851

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.16 kcal/mol

Destabilising · Job 177992460827

PLDDT (ALPHAFOLD)

85.44

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/03/30 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	E385K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-Related Spectrum Disorders
- Monogenic diabetes

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| = 0.16. AlphaMissense 0.851 + multi-phenotype confirm severe consequence.

Mechanism: charge-flip in the L382-E385 loop. Therapeutic: same loop region as L382P.

E385K + L382P converge on the 381-386 loop — multi-variant target.