

# WFS1 N335K — Wolframin

Asparagine → Lysine at position 335. Cytoplasmic loop 1. ClinVar Uncertain significance, AlphaMissense 0.725, DynaMut2  $\Delta\Delta G$  +0.21 kcal/mol (stabilising).

## IDENTITY

|                   |                               |
|-------------------|-------------------------------|
| Variant           | N335K (p.Asparagine335Lysine) |
| DNA change        | c.1005C>A                     |
| Gene · Protein    | WFS1 · Wolframin (890 aa)     |
| UniProt           | O76024 · WFS1_HUMAN           |
| ClinVar accession | VCV003368576                  |
| Amino acid change | Asparagine (N) → Lysine (K)   |

## STRUCTURAL CONTEXT

|                      |  |
|----------------------|--|
| AlphaFold model      | AF-O76024-F1, v6   |
| pLDDT at residue 335 | <b>66.25</b> <span>CONFIDENT</span>  |
| Domain               | Cytoplasmic loop 1   |
| Position context     | Loop region · position 335 sits between transmembrane segments, solvent-accessible |
| IDR flag             | No — pLDDT well above 50 threshold   |

Position 335 sits in a connecting loop between transmembrane helices. Loop residues are typically solvent-exposed and often contribute to interhelical contacts or serve as recognition sites for binding partners. The wild-type residue is polar amide (asparagine — H-bond donor/acceptor); the mutant is positively charged (lysine — primary amine). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.725**

am\_class: **likely pathogenic** —  
threshold > 0.564

DYNAMUT2  $\Delta\Delta G$ **0.21** kcal/mol

Stabilising · Job 178092124109

PLDDT (ALPHAFOLD)

**66.25**

confident

## CLINICAL EVIDENCE

|                        |  |
|------------------------|--|
| ClinVar classification | UNCERTAIN SIGNIFICANCE   |
| Review status          | criteria provided, single submitter  |
| Last evaluated         | 2024/02/01 00:00   |
| Inheritance            | Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.   |
| WFS1 variant landscape | N335K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) <ul style="list-style-type: none"><li>(no conditions catalogued)</li></ul> |

## RESEARCH PATH DECISION TREE

$\Delta\Delta G < 2$  + binding site affected → CATEGORY 3 – docking experiments  $\Delta\Delta G 2-4$  → CATEGORY 2 – pharmacological chaperones  $\Delta\Delta G > 4$  → CATEGORY 1 – gene therapy pLDDT < 50 → CATEGORY 5 – IDR, experimental only Stable fold + functional site hit → CATEGORY 4 – site-specific docking

### Category 3/4 — Most Druggable

$|\Delta\Delta G|=0.21 < 2$  kcal/mol (fold intact) + AlphaMissense 0.725 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframín's fold survives this substitution ( $|\Delta\Delta G|=0.21$  kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.725. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.