

# WFS1 K800N — Wolframin

Lysine → Asparagine at position 800. C-terminal ER-luminal (calcium binding. ClinVar Uncertain significance, AlphaMissense 0.955, DynaMut2  $\Delta\Delta G$  -0.46 kcal/mol (destabilising).

## IDENTITY

|                   |                               |
|-------------------|-------------------------------|
| Variant           | K800N (p.Lysine800Asparagine) |
| DNA change        | c.2400G>C                     |
| Gene · Protein    | WFS1 · Wolframin (890 aa)     |
| UniProt           | O76024 · WFS1_HUMAN           |
| ClinVar accession | VCV003637017                  |
| Amino acid change | Lysine (K) → Asparagine (N)   |

## STRUCTURAL CONTEXT

|                      |   |
|----------------------|---|
| AlphaFold model      | AF-O76024-F1, v6  |
| pLDDT at residue 800 | <b>71.69</b> HIGH CONFIDENCE  |
| Domain               | C-terminal ER-luminal (calcium binding, calmodulin, chaperone)      |
| Position context     | C-terminal luminal domain · position 800 projects into the ER lumen |
| IDR flag             | No — pLDDT well above 50 threshold                                  |

Position 800 sits in the C-terminal luminal domain (residues 653–869), wolframin's largest soluble region. This domain projects into the ER lumen and is implicated in calcium handling, ER stress sensing, and protein–protein interactions with ATF6 and Na<sup>+</sup>/K<sup>+</sup> ATPase  $\beta$ 1. The wild-type residue is positively charged (lysine — primary amine); the mutant is polar amide (asparagine — H-bond donor/acceptor). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.955**am\_class: **likely pathogenic** —  
threshold > 0.564DYNAMUT2  $\Delta\Delta G$ **-0.46** kcal/molDestabilising · Job  
178092099236

PLDDT (ALPHAFOLD)

**71.69**

high confidence

## CLINICAL EVIDENCE

|                        |  |
|------------------------|--|
| ClinVar classification | UNCERTAIN SIGNIFICANCE   |
| Review status          | criteria provided, single submitter  |
| Last evaluated         | 2024/04/25 00:00   |
| Inheritance            | Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.   |
| WFS1 variant landscape | K800N 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

$|\Delta\Delta G|=0.46 < 2$  kcal/mol (fold intact) + AlphaMissense 0.955 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframín's fold survives this substitution ( $|\Delta\Delta G|=0.46$  kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.955. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.