MOLECULAR ATLAS · VARIANT CARD

# WFS1 K596M — Wolframin

Lysine → Methionine at position 596. Cytoplasmic loop 5 / pre-lumenal. ClinVar Uncertain significance, AlphaMissense 0.728, DynaMut2 ΔΔG +0.18 kcal/mol (stabilising).

## IDENTITY

| | |
|---|---|
| Variant | K596M (p.Lysine596Methionine) |
| DNA change | c.1787A>T |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV001695463 |
| Amino acid change | Lysine (K) → Methionine (M) |

## STRUCTURAL CONTEXT

| | |
|---|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 596 | **62.06** CONFIDENT |
| Domain | Cytoplasmic loop 5 / pre-lumenal |
| Position context | C-terminal lumenal domain · position 596 projects into the ER lumen |
| IDR flag | No — pLDDT well above 50 threshold |

> Position 596 sits in the C-terminal lumenal 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+/K+ ATPase β1. The wild-type residue is positively charged (lysine — primary amine); the mutant is hydrophobic sulfur (methionine). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.728**

am_class: **likely pathogenic** — threshold > 0.564

DYNAMUT2 ΔΔG

**0.18** kcal/mol

Stabilising · Job 178092122932

PLDDT (ALPHAFOLD)

**62.06**

confident

## CLINICAL EVIDENCE

| | |
|---|---|
| ClinVar classification | UNCERTAIN SIGNIFICANCE |
| Review status | criteria provided, single submitter |
| Last evaluated | 2022/01/11 00:00 |
| Inheritance | Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations. |
| WFS1 variant landscape | K596M is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- (no conditions catalogued)

---

## RESEARCH PATH DECISION TREE

```
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
```

**Category 3/4 — Most Druggable**

|ΔΔG|=0.18 < 2 kcal/mol (fold intact) + AlphaMissense 0.728 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.18 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.728. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.

---