MOLECULAR ATLAS · VARIANT CARD

WFS1 K836N — Wolframin

Lysine → Asparagine at position 836 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic, rare genetic deafness. AlphaMissense 0.996 (near-maximum), DynaMut2 ΔΔG -0.64 kcal/mol (destabilising). A long-range contact variant — TRP678 sits 3.4 Å away across the lumenal fold.

IDENTITY

Variant	K836N (p.Lysine836Asparagine)
DNA change	c.2508G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000228313
Amino acid change	Lysine (K) → Asparagine (N) — positively-charged primary amine replaced by neutral polar amide. Loss of charge and long side chain; H-bonding preserved.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 836	**81.75** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 836 in the ER lumen (pLDDT 82).
IDR flag	No — pLDDT well above 50 threshold

Position 836 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places K836 within 5 Å of TRP837 (2.5 Å), SER835 (2.5 Å), TRP678 (3.4 Å — long-range cross-domain contact), and PRO838 (5.0 Å). The TRP678 contact is structurally significant — a residue 158 sequence positions away brought into 3.4 Å contact through the folded geometry. The wild-type lysine at 836 likely makes a cation-π interaction with W678's indole ring across this long-range contact. Cation-π interactions are energetically substantial in folded proteins; their loss has measurable consequences. Replacing K836 with asparagine eliminates the positive charge that mediated the cation-π interaction with W678. The new N836 can H-bond to nearby residues but cannot replicate the cation-π geometry. The |ΔΔG| of 0.64 reflects fold

absorption of the lost contact. AlphaMissense's 0.996 + DFNA6 clinical evidence confirm severe functional consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.996	**-0.64** kcal/mol	**81.75**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991409629	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/06/11 00:00
Inheritance	DFNA6 hearing loss documented.
WFS1 variant landscape	K836N is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Rare genetic deafness

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| = 0.64 kcal/mol — fold survives. AlphaMissense 0.996 + DFNA6 confirm severe functional consequence.

The mechanism is loss of a long-range cation-π interaction between K836 and W678 (3.4 Å, 158 sequence positions apart). Therapeutic strategy: site-

directed small molecule bridging the K836-W678 contact across the lumenal fold.

K836N is the Atlas's clearest example of a long-range cation-π interaction loss. The 158-sequence-position separation between contacting residues is invisible to sequence analysis but surfaced cleanly by the AlphaFold-derived neighbor extraction.
