MOLECULAR ATLAS · VARIANT CARD

WFS1 D866N — Wolframin

Aspartate → Asparagine at position 866. ClinVar Conflicting including monogenic diabetes + Wolfram. AlphaMissense 0.18 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.59.

IDENTITY

Variant	D866N (p.Aspartate866Asparagine)
DNA change	c.2596G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000178655
Amino acid change	Aspartate (D) → Asparagine (N) — charge loss; H-bonding preserved.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 866	**63.50** CONFIDENT
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 866 (pLDDT 64 borderline).
IDR flag	No — pLDDT well above 50 threshold

> Position 866 in C-terminal cluster. Neighbors: TRP867 (2.5 Å), HIS865 (2.5 Å — partner of E864K via H865), ARG868 (4.3 Å — R868H!). The 864-868 cluster has E864K, H865 (E864K's neighbor), D866N (this card), R868H — four variants/positions in five residues. D866N charge loss in dense multi-variant cluster. AM 0.18 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.176

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.59 kcal/mol

Destabilising · Job 177992500249

PLDDT (ALPHAFOLD)

63.50

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/28 00:00
Inheritance	Monogenic diabetes + Wolfram.
WFS1 variant landscape	D866N is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic diabetes
- Wolfram syndrome 1

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 (AM under-call). |ΔΔG| 0.59. AlphaMissense 0.18 below threshold but multi-phenotype confirms.

Mechanism: charge loss in dense 864-868 cluster. Therapeutic: same C-terminal cluster.

D866N extends the 864-868 multi-variant cluster — 5+ Atlas variants now in this 5-residue stretch.

RareResearch.AI · WFS1 Molecular Atlas · Generated by wolfram-variant-card skill *Every assumption documented.*