MOLECULAR ATLAS · VARIANT CARD

WFS1 A844V — Wolframin

Alanine → Valine at position 844 in lumenal C-terminal region. ClinVar Conflicting including spastic ataxia. AlphaMissense 0.782, ΔΔG +0.09 (near-neutral).

IDENTITY

Variant	A844V (p.Alanine844Valine)
DNA change	c.2531C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000666957
Amino acid change	Alanine (A) → Valine (V) — small replaced by branched aliphatic. Modest volume increase.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 844	**87.62** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 844 (pLDDT 88).
IDR flag	No — pLDDT well above 50 threshold

Position 844 sits in the lumenal C-terminus. Neighbors: ILE845 (2.4 Å), LYS843 (2.4 Å — partner of K843 cluster from L842F), VAL861 (3.2 Å — long-range; near K862N), SER826 (3.7 Å). The wild-type alanine provides minimal volume. Replacing it with valine introduces branched aliphatic into a pocket sized for alanine. The K843-A844-V861 microregion is perturbed. AM 0.782 + spastic ataxia confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.782

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

0.09 kcal/mol

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PLDDT (ALPHAFOLD)

87.62

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/17 00:00
Inheritance	Spastic ataxia documented.
WFS1 variant landscape	A844V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Spastic ataxia
- Inborn genetic diseases

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 4 — Stable Fold, Function Disrupted. ΔΔG near-neutral. AlphaMissense 0.782 + spastic ataxia confirm severe consequence.

Mechanism: volume mismatch in the K843-V861 long-range microregion. Therapeutic: site-directed at the C-terminal cluster (with L842F, K862N targets).

A844V joins L842F and K862N as variants in the K843-V861 long-range cluster.