

WFS1 V839A — Wolframin

Valine → Alanine at position 839 in luminal domain. ClinVar Conflicting including Wolfram syndrome 1. AlphaMissense 0.398 (below threshold), $\Delta\Delta G$ -1.37 (substantial destabilising).

IDENTITY

Variant	V839A (p.Valine839Alanine)
DNA change	c.2516T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000505203
Amino acid change	Valine (V) → Alanine (A) — branched aliphatic replaced by small methyl-bearing. Volume decrease.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 839	87.69 HIGH CONFIDENCE
Domain	C-terminal luminal domain (653-869)
Position context	C-terminal luminal domain · position 839 (pLDDT 88).
IDR flag	No — pLDDT well above 50 threshold

Position 839 in luminal domain. Neighbors: PHE840 (2.4 Å — partner of L842F, L829P regions), PRO838 (2.5 Å), VAL803 (3.3 Å — long-range; L804P region), TRP837 (4.3 Å). Replacing V839 with alanine reduces side-chain volume substantially, creating a cavity. The V803 long-range contact through the fold geometry is perturbed. $|\Delta\Delta G|$ 1.37 reflects substantial fold cost. AM 0.398 below threshold; Wolfram 1 confirms pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.398am_class: **Amb** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$

PLDDT (ALPHAFOLD)

87.69

high confidence

-1.37 kcal/

mol

Destabilising · Job
177992475434

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2024/02/24 00:00

Inheritance

Wolfram syndrome 1.

WFS1 variant landscape

V839A is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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 (AM under-call). $|\Delta\Delta G|$ 1.37 substantial. AlphaMissense 0.398 below threshold but Wolfram 1 + $\Delta\Delta G$ confirm pathogenicity.

Mechanism: hydrophobic cavity creation + V839-V803 long-range contact perturbation. Therapeutic: luminal hub region (with L842F, L829P, L804P targets).

V839A joins the 829-844 luminal cluster — multiple variants converge.