MOLECULAR ATLAS · VARIANT CARD

WFS1 A326V — Wolframin

Alanine → Valine at position 326 inside TM1. ClinVar Conflicting for Wolfram syndrome 1. AlphaMissense 0.29 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.03 kcal/mol (neutral). Third Atlas substitution at position 326 (with A326E, A326T).

IDENTITY

Variant	A326V (p.Alanine326Valine)
DNA change	c.977C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000592987
Amino acid change	Alanine (A) → Valine (V) — small methyl replaced by branched aliphatic. Conservative volume increase.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 326	**76.88** HIGH CONFIDENCE
Domain	TM1 (314-334), helical transmembrane
Position context	TM1 (residues 314–334) · position 326 (pLDDT 77). Same as A326E, A326T.
IDR flag	No — pLDDT well above 50 threshold

> Position 326 same neighbors as A326E/A326T: ASN325 (2.5 Å), LEU327 (2.5 Å), HIS322 (3.6 Å — H323R neighbor cluster). The H322-H323-A326 microregion is a multi-variant hub in TM1. A326V is the most conservative substitution at position 326 (with A326E charge introduction and A326T polar introduction). All three pathogenic — position 326 is structurally inflexible regardless of substitution chemistry.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.288		**76.88**

am_class: **LBen** — threshold > 0.564

-0.03 kcal/ mol

Destabilising · Job 177992494194

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/11/27 00:00
Inheritance	Wolfram syndrome 1.
WFS1 variant landscape	A326V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- 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 4 — Stable Fold, Function Disrupted (AM under-call). $\Delta\Delta G \approx 0$. AlphaMissense 0.29 below threshold but Wolfram 1 + dual-position substitutions confirm pathogenicity.

Therapeutic strategy: same TM1 H322-H323-A326 microregion as A326E, A326T, H323R.

A326V completes the THIRD substitution at position 326 (with A326E, A326T) — multi-substitution hotspot.