MOLECULAR ATLAS · VARIANT CARD

WFS1 V412A — Wolframin

Valine → Alanine at position 412 inside TM3. ClinVar Conflicting including WFS1 spectrum. AlphaMissense 0.395 (below threshold), ΔΔG -1.23. Same position as V412L — second substitution at 412.

IDENTITY

Variant	V412A (p.Valine412Alanine)
DNA change	c.1235T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215387
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 412	**93.69** HIGH CONFIDENCE
Domain	TM3 (402-422), helical transmembrane
Position context	TM3 (residues 402–422) · position 412 (pLDDT 94).
IDR flag	No — pLDDT well above 50 threshold

Position 412 same neighbors as V412L: PHE413 (2.5 Å), SER411 (2.5 Å), LEU409 (3.8 Å), PHE408 (3.9 Å — TM3-TM7 interface position). V412A is the more drastic substitution at 412 (vs the conservative V412L). Volume loss creates cavity in TM3. The F408 cross-helix contact is perturbed. |ΔΔG| 1.23 substantial. AM 0.395 below threshold but WFS1 spectrum confirms pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.395

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

PLDDT (ALPHAFOLD)

93.69

high confidence

-1.23 kcal/mol

Destabilising · Job 177992474315

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/22 00:00
Inheritance	WFS1 spectrum.
WFS1 variant landscape	V412A is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-Related Spectrum Disorders

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| 1.23 substantial. AlphaMissense 0.395 below threshold but WFS1 spectrum + ΔΔG confirm pathogenicity.

Mechanism: cavity creation in TM3 + F408 cross-helix disruption. Therapeutic: same TM3-TM7 interface as V412L.

V412A + V412L at same position. Both AM under-calls; both target TM3-TM7 interface at F408.