MOLECULAR ATLAS · VARIANT CARD

WFS1 V412L — Wolframin

Valine → Leucine at position 412 inside TM3. ClinVar Conflicting. AlphaMissense 0.663, ΔΔG -0.47. Same position as V412A. Conservative branched-aliphatic swap.

IDENTITY

Variant	V412L (p.Valine412Leucine)
DNA change	c.1234G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000143131
Amino acid change	Valine (V) → Leucine (L) — branched aliphatic to branched aliphatic. Modest volume increase.

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 in TM3. Neighbors: PHE413 (2.5 Å), SER411 (2.5 Å), LEU409 (3.8 Å), PHE408 (3.9 Å — TM3-TM7 interface position). Replacing V412 with leucine is the most conservative substitution at this position. Yet ΔΔG -0.47 + AM 0.663 + WFS1 spectrum confirm pathogenicity. Mechanism is volume mismatch with surrounding F413, S411 environment and perturbation of the F408 TM3-TM7 contact.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.663 am_class: **LPath** — threshold > 0.564	**-0.47** kcal/mol	**93.69** high confidence

Destabilising · Job 177992466151

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2024/09/23 00:00
Inheritance	WFS1 spectrum.
WFS1 variant landscape	V412L 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. |ΔΔG| = 0.47. AlphaMissense 0.663 confirms pathogenicity.

Mechanism: conservative volume mismatch in TM3 + F408 interface perturbation. Therapeutic: TM3-TM7 interface.

V412L + V412A at same position — both pathogenic despite extremely conservative chemistry. Position 412 in TM3 is structurally inflexible.
