MOLECULAR ATLAS · VARIANT CARD

WFS1 V412D — Wolframin

Valine → Aspartic acid at position 412. Transmembrane helix 4. ClinVar Uncertain significance, AlphaMissense 0.965, DynaMut2 ΔΔG -2.42 kcal/mol (destabilising).

IDENTITY

Variant	V412D (p.Valine412Aspartic acid)
DNA change	c.1235T>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001317197
Amino acid change	Valine (V) → Aspartic acid (D)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 412	**93.69** HIGH CONFIDENCE
Domain	Transmembrane helix 4
Position context	Inside Transmembrane helix 4 · position 412 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

> Position 412 sits in a transmembrane helix (Transmembrane helix 4). Wolframin has eleven such helices anchoring it in the ER membrane; substitutions inside the bilayer-embedded segments can disrupt helix packing, lipid contacts, and the overall ER topology of the protein. The wild-type residue is small hydrophobic (valine — branched); the mutant is negatively charged (aspartate — carboxylate). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.965

am_class: **likely pathogenic** — threshold > 0.564

DYNAMUT2 ΔΔG

-2.42 kcal/mol

Destabilising · Job 178092098285

PLDDT (ALPHAFOLD)

93.69

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2026/01/20 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	V412D is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- 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 2 — Moderately Destabilizing

$|\Delta\Delta G|=2.42$ in the 2–4 range. Pharmacological chaperone candidate.