

WFS1 F413V — Wolframin

Phe→Val p413 TM3 AM=0.05 ddg=-0.42 pLDDT=92. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	F413V (p.Phenylalanine413Valine)
DNA change	c.1237T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000166584
Amino acid change	aromatic loss + volume reduction

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 413	91.69 HIGH CONFIDENCE
Domain	TM3 (402-422), helical transmembrane
Position context	TM3 (402-422)
IDR flag	No — pLDDT well above 50 threshold

Position analysis: VAL412 (2.5 Å — V412L/V412A!), PHE414 (2.5 Å — adjacent existing F, also TM3-TM10 contact partner of T641K!), LEU410 (3.8 Å). Multi-variant TM3 cluster. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.055am_class: **LBen** —
threshold > 0.564

DYNAMUT2 ΔΔG

-0.42 kcal/

mol

Destabilising · Job
177992530286

PLDDT (ALPHAFOLD)

91.69

high confidence

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2026/01/24 00:00

Inheritance

Conflicting ClinVar classifications.

WFS1 variant landscape

F413V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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

Cat 3/4 — see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally identified. Therapeutic strategy: site-directed at contacts identified above, or wet-lab validation if pLDDT borderline/below 50.

TM3 cluster (V412L/A + F413V) — also F414 connects to TM10 T641K.