MOLECULAR ATLAS · VARIANT CARD

WFS1 A406D — Wolframin

Alanine → Aspartic acid at position 406. Transmembrane helix 4. ClinVar Uncertain significance, AlphaMissense 0.902, DynaMut2 ΔΔG -0.98 kcal/mol (destabilising).

IDENTITY

Variant	A406D (p.Alanine406Aspartic acid)
DNA change	c.1217C>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003061672
Amino acid change	Alanine (A) → Aspartic acid (D)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 406	**88.38** HIGH CONFIDENCE
Domain	Transmembrane helix 4
Position context	Inside Transmembrane helix 4 · position 406 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 406 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 (alanine — methyl sidechain); 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

0.902

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

DYNAMUT2 ΔΔG

-0.98 kcal/mol

Destabilising · Job 178092107109

PLDDT (ALPHAFOLD)

88.38

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2026/01/14 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	A406D is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no conditions catalogued)

RESEARCH PATH DECISION TREE

```
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
```

Category 3/4 — Most Druggable

|ΔΔG|=0.98 < 2 kcal/mol (fold intact) + AlphaMissense 0.902 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.98 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.902. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
