MOLECULAR ATLAS · VARIANT CARD

WFS1 A422P — Wolframin

Alanine → Proline at position 422. Lumenal loop 2. ClinVar Uncertain significance, AlphaMissense 0.945, DynaMut2 ΔΔG +0.62 kcal/mol (stabilising).

IDENTITY

Variant	A422P (p.Alanine422Proline)
DNA change	c.1264G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003590687
Amino acid change	Alanine (A) → Proline (P)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 422	**87.12** HIGH CONFIDENCE
Domain	Lumenal loop 2
Position context	C-terminal lumenal domain · position 422 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

> Position 422 sits in the C-terminal lumenal domain (residues 653–869), wolframin's largest soluble region. This domain projects into the ER lumen and is implicated in calcium handling, ER stress sensing, and protein–protein interactions with ATF6 and Na+/K+ ATPase β1. The wild-type residue is small/hydrophobic (alanine — methyl sidechain); the mutant is rigid/helix-breaking (proline — kinks backbone). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.945

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

DYNAMUT2 ΔΔG

0.62 kcal/mol

Stabilising · Job 178092141883

PLDDT (ALPHAFOLD)

87.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2024/01/31 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	A422P is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Autosomal dominant nonsyndromic hearing loss 6
- Cataract 41
- Wolfram syndrome 1
- Wolfram-like syndrome
- Type 2 diabetes mellitus

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|=0.62 < 2 kcal/mol (fold intact) + AlphaMissense 0.945 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.62 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.945. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
