MOLECULAR ATLAS · VARIANT CARD

WFS1 A806P — Wolframin

Alanine → Proline at position 806 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic/Likely pathogenic. AlphaMissense 0.991, DynaMut2 ΔΔG +0.70 kcal/mol — STABILISING. A proline-introduction variant where the fold tightens but the backbone geometry shifts.

IDENTITY

Variant	A806P (p.Alanine806Proline)
DNA change	c.2416G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001073764
Amino acid change	Alanine (A) → Proline (P) — small methyl-bearing hydrophobic replaced by rigid helix-breaking residue. Backbone constraint introduced.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 806	**90.88** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 806 in the ER lumen (pLDDT 91, high confidence).
IDR flag	No — pLDDT well above 50 threshold

Position 806 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places A806 within 5 Å of SER807 (2.4 Å), ARG805 (2.4 Å), PHE775 (3.8 Å — long-range), PHE810 (4.1 Å), and LEU842 (4.2 Å). The local environment is mixed polar-aromatic, with two distant phenylalanines (F775, F810) and a long-range leucine (L842) all within structural contact. The wild-type alanine at 806 contributes minimal side-chain mass. Replacing it with proline introduces a forced backbone kink where the wild-type allowed a smooth helical or extended conformation. The DynaMut2 ΔΔG of +0.70 (stabilising) reflects that the new proline-induced geometry happens to pack slightly more efficiently against the surrounding aromatic cluster — but the precise wild-type backbone geometry is gone. AlphaMissense's 0.991 score confirms severe functional consequence despite the structural stabilization. The mechanism is geometric: the F775-A806-F810-L842 packing arrangement that the wild-type backbone maintained is shifted by the

introduced proline kink. Drug discovery targets the multi-residue contact rather than the position alone.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.991	**0.7** kcal/mol	**90.88**
am_class: **LPath** — threshold > 0.564	Stabilising · Job 177991404561	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2023/07/31 00:00
Inheritance	Inheritance not specified. ClinVar Pathogenic/ Likely pathogenic with multiple submitters.
WFS1 variant landscape	A806P is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for A806P — ClinVar P/LP by review evidence)

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 4 — Stable Fold, Function Disrupted. ΔΔG = +0.70 kcal/mol stabilising. AlphaMissense 0.991 confirms severe functional consequence despite the structural gain.

The mechanism is loss of wild-type backbone geometry through proline-introduction in a multi-aromatic contact region (F775, F810). Therapeutic strategy: site-directed at the A806-F810-F775-L842 contact cluster.

A806P joins the Atlas's stabilising-but-pathogenic class (T361I, L402P, R685P, E809K). The pattern across this class is consistent — substitutions that improve local packing energetically but break functional geometry. ΔΔG alone misses them entirely; the dual-metric framing catches them.
