MOLECULAR ATLAS · VARIANT CARD

WFS1 A433P — Wolframin

Alanine → Proline at position 433 inside TM4. ClinVar Likely pathogenic, optic atrophy. AlphaMissense 0.990, DynaMut2 ΔΔG -0.05 kcal/mol — essentially neutral. A proline-introduction in a TM helix where the fold barely registers but function is severely disrupted.

IDENTITY

Variant	A433P (p.Alanine433Proline)
DNA change	c.1297G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003250063
Amino acid change	Alanine (A) → Proline (P) — small methyl-bearing residue replaced by rigid helix-breaking residue.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 433	**91.31** HIGH CONFIDENCE
Domain	TM4 (427-447), helical transmembrane
Position context	TM4 (residues 427–447) · position 433 mid-helix, bilayer-embedded (pLDDT 91).
IDR flag	No — pLDDT well above 50 threshold

Position 433 sits in the middle of TM4. The AlphaFold model places A433 within 5 Å of VAL434 (2.5 Å), LEU432 (2.5 Å), THR436 (3.3 Å), CYS429 (3.6 Å), and ILE547 (4.0 Å — TM4-TM7 cross-helix contact). The hydrophobic core packing here is tight. Introducing proline at 433 in the middle of a TM helix is structurally severe — even though DynaMut2 reports near-zero ΔΔG. The helix's α-helical hydrogen-bond network is broken at the proline (proline cannot donate the backbone amide H-bond that helices require). The helix either kinks at 433 or partially unwinds locally. The TM4-TM7 cross-helix contact at I547 (4.0 Å) is materially perturbed. The near-zero ΔΔG reflects that the fold finds a way to absorb the proline insertion through local rearrangement. AlphaMissense's 0.990 + optic atrophy clinical evidence confirm severe functional consequence. The variant is one of multiple TM4-proline variants in the Atlas (with P428R, P504L family).

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.990	**-0.05** kcal/mol	**91.31**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991410826	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	no assertion criteria provided
Last evaluated	2019/01/01 00:00
Inheritance	Optic atrophy documented.
WFS1 variant landscape	A433P is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Optic atrophy

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| = 0.05 — fold essentially unchanged. AlphaMissense 0.990 + optic atrophy confirm severe functional consequence.

The mechanism is α-helical H-bond network disruption inside TM4 plus perturbation of the TM4-TM7 cross-helix contact (I547). Therapeutic strategy: site-directed at the TM4-TM7 interface.

A433P is another TM-helix proline-introduction variant. The Atlas now contains a cluster of these (L402P, A433P, L543P, L723P, L804P, L829P) that together establish the mechanism class as a coherent target category.