MOLECULAR ATLAS · VARIANT CARD

WFS1 P346L — Wolframin

Proline → Leucine at position 346 inside TM2. ClinVar Conflicting with broad clinical spectrum — Wolfram syndrome 1, Cataract 41, Wolfram-like syndrome. AlphaMissense 0.917, ΔΔG -0.62.

IDENTITY

Variant	P346L (p.Proline346Leucine)
DNA change	c.1037C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000229634
Amino acid change	Proline (P) → Leucine (L) — rigid helix-breaking residue replaced by branched aliphatic hydrophobic. Removes backbone constraint.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 346	**87.62** HIGH CONFIDENCE
Domain	TM2 (340-360), helical transmembrane
Position context	TM2 (residues 340–360) · position 346 mid-helix (pLDDT 88).
IDR flag	No — pLDDT well above 50 threshold

Position 346 sits in TM2. Neighbors: ILE345 (2.5 Å), LEU347 (2.5 Å), ILE349 (4.4 Å — partner of F350I/I349 cluster), PHE344 (4.4 Å). The local environment is uniformly hydrophobic, characteristic of a bilayer-embedded helix interior. The wild-type proline at 346 likely defines a controlled kink in TM2's middle. Replacing it with leucine removes the kink and lets the helix straighten. The |ΔΔG| of 0.62 reflects modest fold cost; AlphaMissense 0.917 + Wolfram 1 + Cataract 41 confirm severe multi-tissue consequence. The variant is in the broader F350I TM2 cluster.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)

0.917
am_class: **LPath** — threshold > 0.564

-0.62 kcal/mol
Destabilising · Job 177992456955

87.62
high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2024/10/26 00:00
Inheritance	Wolfram syndrome 1, Wolfram-like syndrome, Cataract 41 documented.
WFS1 variant landscape	P346L is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1
- Cataract 41
- Wolfram-like syndrome

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 3/4 — Most Druggable. |ΔΔG| = 0.62 — fold survives. AlphaMissense 0.917 + three documented phenotypes confirm severe consequence.

Mechanism: loss of TM2 helix kink. Therapeutic: TM2 site-directed (same broader region as F350I).

P346L is the second TM2 variant in the Atlas (with F350I), establishing TM2 as a target region.