MOLECULAR ATLAS · VARIANT CARD

WFS1 P885L — Wolframin

Proline → Leucine at position 885 inside wolframin's eleventh and final transmembrane helix (TM11). ClinVar Pathogenic/Likely pathogenic with the broadest clinical spectrum documented for any single position in the gene: Wolfram syndrome 1, Wolfram-like syndrome, DFNA6 hearing loss, Cataract 41, type 2 diabetes. AlphaMissense 0.971, DynaMut2 ΔΔG -0.50 kcal/mol (destabilising).

IDENTITY

Variant	P885L (p.Proline885Leucine)
DNA change	c.2654C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000437297
Amino acid change	Proline (P) → Leucine (L) — a rigid, ring-locked, helix-breaking residue replaced by a flexible, branched hydrophobic. The substitution removes a deliberate helix kink from a transmembrane segment.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 885	**74.19** HIGH CONFIDENCE
Domain	TM11 (870-890), helical transmembrane
Position context	TM11 (residues 870–890) · position 885 is bilayer-embedded near the C-terminus of wolframin, where TM11 anchors the lumenal domain to the membrane. pLDDT 74 indicates good local confidence in the AlphaFold model.
IDR flag	No — pLDDT well above 50 threshold

Position 885 sits inside TM11, the final transmembrane helix of wolframin. The AlphaFold model places P885 within 5 Å of PHE886 (2.5 Å), PHE884 (2.5 Å), PHE883 (4.2 Å), and LEU887 (4.7 Å). The local environment is dominated by aromatic residues — an aromatic cluster (F883, F884, F886) within a single membrane-embedded turn of helix. The wild-type proline at position 885 is structurally deliberate. Proline residues in transmembrane helices appear in specific positions where the protein needs the helix to kink — they introduce a controlled bend in what would otherwise be a straight α-helix.

Proline at position 885, sitting in the middle of three consecutive phenylalanines, almost certainly serves this kinking role: it creates a controlled local geometry that the surrounding aromatic packing depends on. Replacing proline with leucine removes that controlled kink. Leucine cannot break the helix in the same way — its backbone is free to adopt the standard α-helical phi/psi angles. The result is a TM11 that is more linear than the wild-type, with the aromatic cluster (F883, F884, F886) reorganized accordingly. The interlocking packing that depends on the wild-type kink is lost. The |ΔΔG| of 0.50 kcal/mol indicates the fold absorbs this rearrangement — TM11 still embeds in the membrane, the protein still folds. But the precise geometry of the C-terminal anchoring region is changed, and the AlphaMissense score of 0.971 reflects severe functional consequence. Notably, C505Y (Atlas card adjacent, in TM6) has PRO885 as a 4.1 Å neighbor — suggesting TM6-TM11 cross-talk in the membrane. Disrupting the P885 kink also affects whatever functional contact TM6 makes through this position.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.971	**-0.5** kcal/mol	**74.19**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991404199	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/06/04 00:00
Inheritance	Both autosomal dominant (DFNA6, Wolfram-like) and autosomal recessive (Wolfram syndrome 1) forms documented. The breadth of clinical conditions makes this one of the most clinically impactful variants in the Atlas.
WFS1 variant landscape	P885L is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1
- Wolfram-like syndrome
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)
- Cataract 41

- Type 2 diabetes mellitus

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| = 0.50 kcal/mol — fold survives. AlphaMissense 0.971 + five documented clinical phenotypes confirm severe functional consequence.

The mechanism is loss of a deliberate proline-induced helix kink in TM11, perturbing the C-terminal membrane anchoring geometry and disrupting the TM6-TM11 cross-helix contact through C505/P885 (see C505Y Atlas card for the reciprocal view).

The therapeutic strategy is site-directed at the TM11 aromatic cluster: a small molecule that restores the helix geometry the wild-type kink produced, or that occupies the disrupted TM6-TM11 interface, would compensate for the lost kink. The clinical breadth (five distinct phenotypes documented) makes this one of the highest-value docking targets in the WFS1 atlas.

P885L exemplifies how the atlas's structural reasoning surfaces non-obvious therapeutic targets. The variant's pathogenicity is well-established clinically; what was not visible without the structural map is that TM11's geometry depends on a deliberate proline kink, and disrupting it perturbs the TM6-TM11 interface across the membrane. C505Y in the Atlas points back to this same interface from the TM6 side. A drug aimed at the TM6-TM11 contact rescues both variants — and likely several others in the same region.
