MOLECULAR ATLAS · VARIANT CARD

# WFS1 P504L — Wolframin

Proline → Leucine at position 504 inside wolframin's sixth transmembrane helix (TM6). ClinVar Pathogenic with the broadest clinical spectrum in the gene — Wolfram syndrome 1, Wolfram-like syndrome, DFNA6 hearing loss, Cataract 41, type 2 diabetes. AlphaMissense 0.797, DynaMut2 ΔΔG -0.56 kcal/mol (destabilising). One of two adjacent variants (with C505Y) characterizing a vulnerable TM6 region.

## IDENTITY

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|---|---|
| Variant | P504L (p.Proline504Leucine) |
| DNA change | c.1511C>T |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV000004512 |
| Amino acid change | Proline (P) → Leucine (L) — a rigid, helix-breaking residue replaced by a flexible, branched hydrophobic. The substitution removes a deliberate helix kink from a transmembrane segment. |

## STRUCTURAL CONTEXT

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|---|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 504 | **82.88** HIGH CONFIDENCE |
| Domain | TM6 (496-516), helical transmembrane |
| Position context | TM6 (residues 496–516) · position 504 is bilayer-embedded, immediately preceding C505 in the helix sequence. Together with C505 it sits at a structurally critical region of TM6. |
| IDR flag | No — pLDDT well above 50 threshold |

Position 504 sits inside TM6, immediately adjacent to C505 (Atlas card adjacent). The AlphaFold model places P504 within 5 Å of VAL503 (2.5 Å), CYS505 (2.5 Å), SER502 (4.1 Å), PRO885 (4.1 Å, from TM11 — same cross-helix contact as C505/P885), LEU507 (4.3 Å), and LEU506 (4.5 Å). The proline at position 504 occupies the same structural micro-environment as the C505 next to it, and both contact PRO885 in TM11 at ~4.1 Å. The wild-type proline at 504 plays a deliberate kinking role in TM6. Just as P885 kinks TM11 (see P885L Atlas card), P504 introduces a controlled helix bend in TM6. This is structurally remarkable: TM6 contains a proline-induced kink at position 504,

TM11 contains a proline-induced kink at position 885, and the two kinks face each other across the membrane at the C505/P885 interface. The geometry suggests an intentional structural register that the protein's evolutionary design depends on. Replacing the TM6 proline with leucine removes the helix kink — TM6 becomes more linear than the wild-type. The PRO885 in TM11 remains in place, but its docking partner across the helix interface has changed shape. The TM6-TM11 register slips. DynaMut2 reports a |ΔΔG| of 0.56 kcal/mol — the fold absorbs it, but the geometric relationship across the helix interface is materially perturbed. The clinical breadth of P504L (five documented phenotypes spanning both AD and AR Wolfram presentations) is striking given the AlphaMissense score of 0.797 is the lowest of any variant in this batch. The disconnect suggests AlphaMissense's training is conservative about proline substitutions; the clinical evidence is overwhelming.

## COMPUTATIONAL PREDICTIONS

| ALPHAMISSENSE | DYNAMUT2 ΔΔG | PLDDT (ALPHAFOLD) |
|---|---|---|
| **0.796** | **-0.56** kcal/mol | **82.88** |
| am_class: **LPath** — threshold > 0.564 | Destabilising · Job 177990265487 | high confidence |

## CLINICAL EVIDENCE

| | |
|---|---|
| ClinVar classification | **PATHOGENIC** |
| Review status | criteria provided, multiple submitters, no conflicts |
| Last evaluated | 2026/01/12 00:00 |
| Inheritance | Both autosomal dominant (DFNA6, Wolfram-like syndrome) and autosomal recessive (classical Wolfram syndrome 1) presentations documented. Among the most clinically validated WFS1 variants by case count. |
| WFS1 variant landscape | P504L 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)
- Type 2 diabetes mellitus

- Cataract 41

## 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| = 0.56 kcal/mol — fold survives. AlphaMissense 0.797 is in the likely-pathogenic range; the broad clinical spectrum (five phenotypes) confirms severe functional consequence.

The mechanism is removal of a deliberate TM6 helix kink, slipping the TM6-TM11 register at the C505/P504/P885 interface. The therapeutic strategy is geometric: a small molecule that stabilizes the TM6-TM11 packing in the wild-type kink geometry, ideally engaging both sides of the interface (TM6 and TM11) simultaneously.

Compare with P885L (Atlas card adjacent) for the reciprocal mechanism, and with C505Y for an alternative TM6 substitution at the same interface. Three Atlas variants (P504L, C505Y, P885L) converge on a single therapeutic target.

P504L exemplifies why the Atlas's neighbor analysis matters: the variant's mechanism is invisible from sequence alone but visible from structure. P504, C505, and P885 form a three-residue cross-helix register that is required for TM6-TM11 geometry. Three variants in the Atlas (P504L, C505Y, P885L) perturb this register through different substitutions. A drug that rescues one rescues all three — and likely several other variants in the same region not yet in the Windsor Set.