MOLECULAR ATLAS · VARIANT CARD

WFS1 C505Y — Wolframin

Cysteine → Tyrosine at position 505 inside wolframin's sixth transmembrane helix (TM6). ClinVar Pathogenic, associated with diabetes mellitus. AlphaMissense 0.892 (deep pathogenic range), DynaMut2 ΔΔG -0.81 kcal/mol (destabilising). A bilayer-embedded variant with a TM6-TM11 cross-helix mechanism.

IDENTITY

Variant	C505Y (p.Cysteine505Tyrosine)
DNA change	c.1514G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000918063
Amino acid change	Cysteine (C) → Tyrosine (Y) — a small thiol-bearing residue replaced by a large aromatic ring carrying a hydroxyl group. Loss of disulfide-bond capacity and a substantial volume increase, plus introduction of an H-bond donor/acceptor inside a hydrophobic membrane.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 505	**82.44** HIGH CONFIDENCE
Domain	TM6 (496-516), helical transmembrane
Position context	TM6 (residues 496–516) · position 505 is bilayer-embedded. The hydrophobic membrane core penalizes the introduced tyrosine hydroxyl, which prefers polar or aqueous environments.
IDR flag	No — pLDDT well above 50 threshold

Position 505 sits inside TM6, one of wolframin's eleven transmembrane helices. The AlphaFold model places C505 within 5 Å of PRO504 (2.5 Å), LEU506 (2.5 Å), SER502 (3.6 Å), PRO885 (4.1 Å), VAL503 (4.2 Å), and TYR508 (4.3 Å). The most structurally significant neighbor is PRO885 — that's a residue from TM11 (Atlas card P885L adjacent), positioned 4.1 Å away in the AlphaFold structure. This contact indicates that TM6 and TM11 cross each other in the membrane and pack against one another through the C505/P885 region. The wild-type cysteine at position 505 is small and hydrophobic-character — its thiol can either remain free or, in oxidizing

conditions, participate in disulfide formation. The local environment here is bilayer-embedded so disulfide formation is not the dominant mechanism. The wild-type's small volume fits cleanly into the TM6-TM11 packing interface. Replacing cysteine with tyrosine here is unusually disruptive for two reasons. First, the volume increase: tyrosine's aromatic ring is roughly four times the side-chain mass of cysteine. The TM6-TM11 interface, which packs tightly through the C505/P885 region, cannot accommodate the larger side chain without significant rearrangement. Second, the introduced hydroxyl is unfavorable in the bilayer hydrophobic core — it would prefer to point toward the membrane-water interface, dragging the local geometry with it. DynaMut2's |ΔΔG| of 0.81 kcal/mol captures the modest energetic cost of the fold absorbing this rearrangement. But the functional consequence — disrupted TM6-TM11 packing — is more severe than the ΔΔG alone suggests. AlphaMissense's 0.892 score reflects this. Compare with P504L (Atlas card adjacent): proline at position 504 plays a deliberate helix-kinking role, and removing it has its own structural cost. The two variants together — C505Y and P504L — characterize a vulnerable region in TM6 where multiple substitutions produce convergent functional disruption.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.892

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.81 kcal/mol

Destabilising · Job 177990265119

PLDDT (ALPHAFOLD)

82.44

high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	no assertion criteria provided
Last evaluated	1/01/01 00:00
Inheritance	Documented in association with diabetes mellitus. The conservative substitution chemistry and bilayer location suggest the AD-leaning (Wolfram-like, DFNA6) presentation pattern.
WFS1 variant landscape	C505Y is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- 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| = 0.81 kcal/mol — fold survives. AlphaMissense 0.892 confirms deeply pathogenic signal.

The mechanism is disrupted TM6-TM11 helix-helix packing through the C505-P885 contact (4.1 Å in the AlphaFold model). The atlas-surfaced cross-helix interaction makes the therapeutic target geometric: a small molecule that stabilizes the TM6-TM11 interface, occupying the steric niche the wild-type cysteine maintained, would compensate.

The reciprocal Atlas card (P885L) shows the same interface from the TM11 side. Drug discovery targeting this interface has two converging mechanisms it could rescue simultaneously.

C505Y is one of the Atlas's clearest examples of cross-helix contact variants. The pathogenic mechanism is invisible without the AlphaFold-derived neighbor analysis: pre-atlas, C505 looked like a TM6 problem; with the atlas, it's a TM6-TM11 interface problem with a known reciprocal variant (P885L). Drug design at this interface gets reinforced from both sides.