MOLECULAR ATLAS · VARIANT CARD

WFS1 P533S — Wolframin

Proline → Serine at position 533 inside TM7. ClinVar Conflicting classifications including optic atrophy and DFNA6. AlphaMissense 0.979, DynaMut2 ΔΔG -1.33 kcal/mol (destabilising). Proline-removal in TM7 with substantial structural cost.

IDENTITY

Variant	P533S (p.Proline533Serine)
DNA change	c.1597C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000137914
Amino acid change	Proline (P) → Serine (S) — rigid helix-breaking residue replaced by small polar hydroxyl. Removes backbone constraint; adds H-bond capacity.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 533	**84.00** HIGH CONFIDENCE
Domain	TM7 (529-549), helical transmembrane
Position context	TM7 (residues 529–549) · position 533 near the start of TM7 (pLDDT 84).
IDR flag	No — pLDDT well above 50 threshold

Position 533 sits in TM7 near its start. The AlphaFold model places P533 within 5 Å of TYR534 (2.5 Å), VAL532 (2.5 Å), TYR405 (4.0 Å — TM3-TM7 cross-helix!), TYR530 (4.2 Å), and LEU535 (4.4 Å). The TYR405 contact at 4.0 Å is structurally significant — a TM3-TM7 helix-helix interaction through this proline position. The wild-type proline at 533 defines TM7's helix-initiation geometry. Removing it eliminates that controlled kink, freeing the backbone. The introduced serine adds a polar hydroxyl into the bilayer-embedded environment, slightly unfavorable. The |ΔΔG| of 1.33 reflects meaningful fold cost. The TM3-TM7 cross-helix contact at TYR405 is perturbed. AlphaMissense's 0.979 + WFS1-Related Spectrum Disorders + optic atrophy + DFNA6 clinical evidence confirm severe functional consequence across multiple tissue contexts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.979	**-1.33** kcal/mol	**84.00**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992014107	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/03/01 00:00
Inheritance	Both AD (DFNA6) and AR documented.
WFS1 variant landscape	P533S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-Related Spectrum Disorders
- Optic atrophy
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

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| = 1.33 — fold survives at meaningful cost. AlphaMissense 0.979 + three documented phenotypes confirm severe functional consequence.

Mechanism is loss of TM7 helix-initiation geometry plus disruption of TM3-TM7 cross-helix contact at TYR405. Therapeutic strategy: TM3-TM7 interface site-directed.

> P533S identifies a previously-unseen TM3-TM7 interface at the TYR405 contact (4.0 Å). The Atlas surfaces this as a new cross-helix therapeutic target.
