MOLECULAR ATLAS · VARIANT CARD

WFS1 Y508C — Wolframin

Tyrosine → Cysteine at position 508 inside TM6. ClinVar Conflicting including Wolfram. AlphaMissense 0.419 (below threshold), ΔΔG -1.22.

IDENTITY

Variant	Y508C (p.Tyrosine508Cysteine)
DNA change	c.1523A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001027491
Amino acid change	Tyrosine (Y) → Cysteine (C) — large aromatic phenol replaced by small thiol.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 508	**84.75** HIGH CONFIDENCE
Domain	TM6 (496-516), helical transmembrane
Position context	TM6 (residues 496–516) · position 508 (pLDDT 85).
IDR flag	No — pLDDT well above 50 threshold

Position 508 in TM6. Neighbors: LEU507 (2.5 Å), VAL509 (2.5 Å), CYS505 (3.7 Å — C505Y region!), PRO504 (3.8 Å — P504L). The C505 contact at 3.7 Å is structurally significant. Replacing Y508 with cysteine creates a potential new cysteine pair with the adjacent C505. The wild-type Y508 + C505 microregion now becomes a C505 + C508 cluster — two cysteines within 3.7 Å, geometrically capable of forming a new disulfide. This is potentially structurally disruptive. |ΔΔG| 1.22 + AM 0.419 below threshold + Wolfram 1 confirm pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.419		84.75
		high confidence

am_class: **Amb** — threshold > 0.564

-1.22 kcal/mol

Destabilising · Job 177992472799

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2024/01/17 00:00
Inheritance	Wolfram syndrome 1.
WFS1 variant landscape	Y508C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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 (AM under-call). |ΔΔG| 1.22 substantial. AlphaMissense 0.419 below threshold but Wolfram 1 + substantial ΔΔG confirm pathogenicity.

Mechanism: aberrant C505-C508 disulfide creation + lost Y508 aromatic packing. Therapeutic: TM6 P504-C505-Y508 microregion.

Y508C joins the TM6 cluster (P504L, C505Y). Three Atlas variants at three consecutive positions in TM6.