MOLECULAR ATLAS · VARIANT CARD

WFS1 Y528H — Wolframin

Tyrosine → Histidine at position 528. Cytoplasmic loop 4. ClinVar Uncertain significance, AlphaMissense 0.853, DynaMut2 ΔΔG +0.08 kcal/mol (stabilising).

IDENTITY

Variant	Y528H (p.Tyrosine528Histidine)
DNA change	c.1582T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002203522
Amino acid change	Tyrosine (Y) → Histidine (H)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 528	**74.88** HIGH CONFIDENCE
Domain	Cytoplasmic loop 4
Position context	Loop region · position 528 sits between transmembrane segments, solvent-accessible
IDR flag	No — pLDDT well above 50 threshold

> Position 528 sits in a connecting loop between transmembrane helices. Loop residues are typically solvent-exposed and often contribute to interhelical contacts or serve as recognition sites for binding partners. The wild-type residue is aromatic with hydroxyl (tyrosine — H-bond donor/acceptor); the mutant is titratable basic (histidine — imidazole). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.853

am_class: **likely pathogenic** — threshold > 0.564

DYNAMUT2 ΔΔG

0.08 kcal/mol

Stabilising · Job 178092112239

PLDDT (ALPHAFOLD)

74.88

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2022/08/03 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	Y528H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no conditions catalogued)

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|=0.08 < 2 kcal/mol (fold intact) + AlphaMissense 0.853 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.08 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.853. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
