MOLECULAR ATLAS · VARIANT CARD

WFS1 Y291C — Wolframin

Tyrosine → Cysteine at position 291. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance, AlphaMissense 0.865, DynaMut2 ΔΔG +0.55 kcal/mol (stabilising).

IDENTITY

Variant	Y291C (p.Tyrosine291Cysteine)
DNA change	c.872A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000904804
Amino acid change	Tyrosine (Y) → Cysteine (C)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 291	**65.31** CONFIDENT
Domain	N-terminal cytoplasmic (intrinsically disordered)
Position context	N-terminal cytoplasmic (intrinsically disordered)
IDR flag	No — pLDDT well above 50 threshold

> Position 291 sits in N-terminal cytoplasmic (intrinsically disordered). The wild-type residue is aromatic with hydroxyl (tyrosine — H-bond donor/acceptor); the mutant is thiol (cysteine — disulfide-capable, free -SH). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.865

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

DYNAMUT2 ΔΔG

0.55 kcal/mol

Stabilising · Job 178092110512

PLDDT (ALPHAFOLD)

65.31

confident

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2018/01/13 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	Y291C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Autosomal dominant nonsyndromic hearing loss 6
- WFS1-Related Spectrum Disorders
- 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

|ΔΔG|=0.55 < 2 kcal/mol (fold intact) + AlphaMissense 0.865 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.55 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.865. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
