MOLECULAR ATLAS · VARIANT CARD

WFS1 S334R — Wolframin

Serine → Arginine at position 334. Cytoplasmic loop 1. ClinVar Uncertain significance, AlphaMissense 0.986, DynaMut2 ΔΔG -0.19 kcal/mol (destabilising).

IDENTITY

Variant	S334R (p.Serine334Arginine)
DNA change	c.1002C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001331236
Amino acid change	Serine (S) → Arginine (R)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 334	**68.25** CONFIDENT
Domain	Cytoplasmic loop 1
Position context	Loop region · position 334 sits between transmembrane segments, solvent-accessible
IDR flag	No — pLDDT well above 50 threshold

> Position 334 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 small polar (serine — hydroxyl); the mutant is positively charged (arginine — guanidinium, strong H-bond donor). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.986

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

DYNAMUT2 ΔΔG

-0.19 kcal/mol

Destabilising · Job 178092089777

PLDDT (ALPHAFOLD)

68.25

confident

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/05/19 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	S334R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Inborn genetic diseases

RESEARCH PATH DECISION TREE

```
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
```

Category 3/4 — Most Druggable

|ΔΔG|=0.19 < 2 kcal/mol (fold intact) + AlphaMissense 0.986 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.19 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.986. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
