MOLECULAR ATLAS · VARIANT CARD

WFS1 N159S — Wolframin

Asparagine → Serine at position 159. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance, AlphaMissense 0.770, DynaMut2 ΔΔG -0.53 kcal/mol (destabilising).

IDENTITY

Variant	N159S (p.Asparagine159Serine)
DNA change	c.476A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003044331
Amino acid change	Asparagine (N) → Serine (S)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 159	**90.00** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic (intrinsically disordered)
Position context	N-terminal cytoplasmic (intrinsically disordered)
IDR flag	No — pLDDT well above 50 threshold

> Position 159 sits in N-terminal cytoplasmic (intrinsically disordered). The wild-type residue is polar amide (asparagine — H-bond donor/acceptor); the mutant is small polar (serine — hydroxyl). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.770

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

DYNAMUT2 ΔΔG

-0.53 kcal/mol

Destabilising · Job 178092119208

PLDDT (ALPHAFOLD)

90.00

high confidence

CLINICAL EVIDENCE

ClinVar classification — UNCERTAIN SIGNIFICANCE

Review status	no assertion criteria provided
Last evaluated	2023/11/24 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	N159S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-related disorder

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|=0.53 < 2 kcal/mol (fold intact) + AlphaMissense 0.770 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.53 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.770. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
