

WFS1 A671S — Wolframin

Ala→Ser p671 luminal AM=0.06 ddg=+0.05 pLDDT=85. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	A671S (p.Alanine671Serine)
DNA change	c.2011G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000905057
Amino acid change	polarity introduced

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 671	84.56 HIGH CONFIDENCE
Domain	C-terminal luminal domain (653-869)
Position context	C-terminal luminal domain
IDR flag	No — pLDDT well above 50 threshold

Position analysis: GLY670 (2.5 Å — same G670 in G674 cluster!), LEU672 (2.5 Å — L672P!), GLN667 (3.8 Å — same Q667 as Y669 cluster!). Adjacent to G674 + Y669 hubs. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.061am_class: **LBen** —
threshold > 0.564

DYNAMUT2 ΔΔG

0.05 kcal/molStabilising · Job
177992527032

PLDDT (ALPHAFOLD)

84.56

high confidence

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2024/03/28 00:00

Inheritance

Conflicting ClinVar classifications.

WFS1 variant landscape

A671S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

RESEARCH PATH DECISION TREE

$\Delta\Delta G < 2$ + binding site affected \rightarrow CATEGORY 3 – docking experiments $\Delta\Delta G$ 2–4 \rightarrow CATEGORY 2 – pharmacological chaperones $\Delta\Delta G > 4$ \rightarrow CATEGORY 1 – gene therapy pLDDT < 50 \rightarrow CATEGORY 5 – IDR, experimental only Stable fold + functional site hit \rightarrow CATEGORY 4 – site-specific docking

Cat 4 – see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally identified. Therapeutic strategy: site-directed at contacts identified above, or wet-lab validation if pLDDT borderline/below 50.

Adjacent to G674 + Y669 hubs.