MOLECULAR ATLAS · VARIANT CARD

WFS1 H109Y — Wolframin

His→Tyr p109 N-term AM=0.07 ddg=+1.1 pLDDT=92. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	H109Y (p.Histidine109Tyrosine)
DNA change	c.325C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000166570
Amino acid change	aromatic substitution stabilising

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 109	**92.00** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: LYS108 (2.5 Å — same K108 as G107E neighbor!), TYR110 (2.5 Å — adjacent existing Y!), VAL106 (3.6 Å — same V106 as G107E neighbor). Same G107-K108-H109 cluster. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.073

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

1.1 kcal/mol

Stabilising · Job 177992530102

PLDDT (ALPHAFOLD)

92.00

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/10/14 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	H109Y is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific 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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Cat 4 stabilising — 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.

H109Y + G107E in same K108 cluster.

RareResearch.AI · WFS1 Molecular Atlas · Generated by wolfram-variant-card skill *Every assumption documented.*