MOLECULAR ATLAS · VARIANT CARD

WFS1 H407Y — Wolframin

His→Tyr p407 TM3 AM=0.10 ddg=+1.05 pLDDT=90. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	H407Y (p.Histidine407Tyrosine)
DNA change	c.1219C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000166583
Amino acid change	aromatic substitution stabilising

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 407	**90.31** HIGH CONFIDENCE
Domain	TM3 (402-422), helical transmembrane
Position context	TM3 (402-422)
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: PHE408 (2.5 Å — F408 TM3-TM7 interface!), ALA406 (2.5 Å), PRO404 (3.8 Å). Aromatic-rich TM3 environment near F408 cross-helix hub. The Atlas's neighbor extraction surfaces this variant's contacts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE
0.100
am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG
1.05 kcal/mol
Stabilising · Job 177992512525

PLDDT (ALPHAFOLD)
90.31
high confidence

CLINICAL EVIDENCE

ClinVar classification	CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status	criteria provided, conflicting classifications
Last evaluated	2025/12/10 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	H407Y 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 clear from neighbor analysis. Therapeutic strategy: site-directed at the contacts identified above.

TM3 F408 interface variant.
