MOLECULAR ATLAS · VARIANT CARD

WFS1 H313Y — Wolframin

Histidine → Tyrosine at position 313 in wolframin's N-terminal cytoplasmic domain (at the TM1 boundary). ClinVar Pathogenic/Likely pathogenic. AlphaMissense 0.167 (deep BENIGN). DynaMut2 ΔΔG +1.20 kcal/mol — STABILISING. pLDDT 57 borderline. A gray-zone variant.

IDENTITY

Variant	H313Y (p.Histidine313Tyrosine)
DNA change	c.937C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000290817
Amino acid change	Histidine (H) → Tyrosine (Y) — small aromatic titratable basic replaced by larger aromatic phenol. Volume increase; pH-dependent charge replaced by neutral H-bonding hydroxyl.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 313	**57.41** CONFIDENT
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 313 at the boundary with TM1 (W314 begins TM1). pLDDT 57 borderline.
IDR flag	No — pLDDT well above 50 threshold

Position 313 sits at the boundary between wolframin's N-terminal cytoplasmic domain and the start of TM1. The AlphaFold model places H313 within 5 Å of MET312 (2.4 Å), TRP314 (2.5 Å — the start of TM1, partner of W314R Atlas card), SER316 (3.6 Å), ALA310 (3.9 Å), and ARG309 (4.0 Å). The wild-type histidine at 313 plays a boundary role — its titratable imidazole can engage either the cytoplasmic side (with R309) or the membrane interface side (near W314). The variant Y313's larger phenol ring and lack of pH-titration changes this boundary geometry. The ΔΔG of +1.20 (stabilising) reflects the variant fold packs better than wild-type — the introduced tyrosine ring fits the local aromatic environment near W314. But AlphaMissense's 0.167 places this deep in the likely-benign range. ClinVar Pathogenic + the pLDDT 57 borderline confidence together create a

genuinely uncertain variant. This is the most disconnected ΔΔG-vs-AM signal in this batch.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.167	**1.2** kcal/mol	**57.41**
am_class: **LBen** — threshold > 0.564	Stabilising · Job 177991407987	confident

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/10/06 00:00
Inheritance	Inheritance not specified.
WFS1 variant landscape	H313Y is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for H313Y)

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 4 — Stable Fold, Function Disrupted (gray zone). ΔΔG = +1.20 stabilising. AlphaMissense 0.167 deep benign. ClinVar Pathogenic. pLDDT 57 borderline.

The Atlas flags this as a genuinely uncertain variant. Wet-lab validation is strongly recommended before any therapeutic strategy is set.

> H313Y has the most extreme AM-vs-ClinVar disconnect in this batch. The Atlas surfaces the disagreement honestly rather than picking a side. Drug discovery pauses here.
