

# WFS1 H401Y — Wolframin

Histidine → Tyrosine at position 401. Transmembrane helix 4. ClinVar Uncertain significance, AlphaMissense 0.747, DynaMut2  $\Delta\Delta G$  +1.13 kcal/mol (stabilising).

## IDENTITY

Variant	H401Y (p.Histidine401Tyrosine)
DNA change	c.1201C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002134530
Amino acid change	Histidine (H) → Tyrosine (Y)

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 401	<b>81.94</b> HIGH CONFIDENCE
Domain	Transmembrane helix 4
Position context	Inside Transmembrane helix 4 · position 401 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 401 sits in a transmembrane helix (Transmembrane helix 4). Wolframin has eleven such helices anchoring it in the ER membrane; substitutions inside the bilayer-embedded segments can disrupt helix packing, lipid contacts, and the overall ER topology of the protein. The wild-type residue is titratable basic (histidine — imidazole); the mutant is aromatic with hydroxyl (tyrosine — H-bond donor/acceptor). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.747**

am\_class: **likely pathogenic** —  
threshold > 0.564

DYNAMUT2  $\Delta\Delta G$ **1.13** kcal/mol

Stabilising · Job 178092121347

PLDDT (ALPHAFOLD)

**81.94**

high confidence

## CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2023/08/30 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	H401Y is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) <ul style="list-style-type: none"><li>(no conditions catalogued)</li></ul>

## RESEARCH PATH DECISION TREE

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

### Category 3/4 — Most Druggable

$|\Delta\Delta G|=1.13 < 2$  kcal/mol (fold intact) + AlphaMissense 0.747 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution ( $|\Delta\Delta G|=1.13$  kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.747. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.