

WFS1 H766Y — Wolframin

Histidine → Tyrosine at position 766. C-terminal ER-luminal (calcium binding. ClinVar Uncertain significance/Uncertain risk allele, AlphaMissense 0.682, DynaMut2 $\Delta\Delta G$ +1.10 kcal/mol (stabilising).

IDENTITY

Variant	H766Y (p.Histidine766Tyrosine)
DNA change	c.2296C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001328885
Amino acid change	Histidine (H) → Tyrosine (Y)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 766	89.25 HIGH CONFIDENCE
Domain	C-terminal ER-luminal (calcium binding, calmodulin, chaperone)
Position context	C-terminal luminal domain · position 766 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

Position 766 sits in the C-terminal luminal domain (residues 653–869), wolframin's largest soluble region. This domain projects into the ER lumen and is implicated in calcium handling, ER stress sensing, and protein–protein interactions with ATF6 and Na⁺/K⁺ ATPase β 1. 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

0.682am_class: **likely pathogenic** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **1.1** kcal/mol

Stabilising · Job 178092126522

PLDDT (ALPHAFOLD)

89.25

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE/UNCERTAIN RISK ALLELE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2023/03/01 00:00
Inheritance	Autosomal recessive Wolfram syndrome 1 phenotype documented.
WFS1 variant landscape	H766Y is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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

$|\Delta\Delta G|=1.10 < 2$ kcal/mol (fold intact) + AlphaMissense 0.682 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution ($|\Delta\Delta G|=1.10$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.682. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.