

# WFS1 D866Y — Wolframin

Aspartic acid → Tyrosine at position 866. C-terminal ER-luminal (calcium binding. ClinVar Uncertain significance, AlphaMissense 0.599, DynaMut2  $\Delta\Delta G$  +0.16 kcal/mol (stabilising)).

## IDENTITY

Variant	D866Y (p.Aspartic acid866Tyrosine)
DNA change	c.2596G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001367278
Amino acid change	Aspartic acid (D) → Tyrosine (Y)

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 866	<b>63.50</b> <span>CONFIDENT</span>
Domain	C-terminal ER-luminal (calcium binding, calmodulin, chaperone)
Position context	C-terminal luminal domain · position 866 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

Position 866 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<sup>+</sup>/K<sup>+</sup> ATPase  $\beta$ 1. The wild-type residue is negatively charged (aspartate — carboxylate); 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

**0.599**am\_class: **likely pathogenic** —  
threshold > 0.564DYNAMUT2  $\Delta\Delta G$ **0.16** kcal/mol

Stabilising · Job 178092132904

PLDDT (ALPHAFOLD)

**63.50**

confident

## CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/07/14 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	D866Y is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) <ul style="list-style-type: none"><li>• Cataract 41</li><li>• Wolfram syndrome 1</li><li>• Autosomal dominant nonsyndromic hearing loss 6</li><li>• Type 2 diabetes mellitus</li><li>• Wolfram-like syndrome</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

$|\Delta\Delta G|=0.16 < 2$  kcal/mol (fold intact) + AlphaMissense 0.599 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolfram's fold survives this substitution ( $|\Delta\Delta G|=0.16$  kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.599. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.