

WFS1 Y660C — Wolframin

Tyrosine → Cysteine at position 660. C-terminal ER-luminal (calcium binding. ClinVar Uncertain significance, AlphaMissense 0.960, DynaMut2 $\Delta\Delta G$ +0.87 kcal/mol (stabilising).

IDENTITY

Variant	Y660C (p.Tyrosine660Cysteine)
DNA change	c.1979A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002062418
Amino acid change	Tyrosine (Y) → Cysteine (C)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 660	62.75 CONFIDENT
Domain	C-terminal ER-luminal (calcium binding, calmodulin, chaperone)
Position context	C-terminal luminal domain · position 660 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

Position 660 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 aromatic with hydroxyl (tyrosine — H-bond donor/acceptor); the mutant is thiol (cysteine — disulfide-capable, free -SH). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.960am_class: **likely pathogenic** — threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **0.87** kcal/mol

Stabilising · Job 178092098459

PLDDT (ALPHAFOLD)

62.75

confident

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2022/08/16 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	Y660C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) <ul style="list-style-type: none">(no conditions catalogued)

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

$|\Delta\Delta G|=0.87 < 2$ kcal/mol (fold intact) + AlphaMissense 0.960 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframins fold survives this substitution ($|\Delta\Delta G|=0.87$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.960. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.