

WFS1 C360Y — Wolframin

Cysteine → Tyrosine at position 360. Transmembrane helix 2. ClinVar Uncertain significance, AlphaMissense 0.980, DynaMut2 $\Delta\Delta G$ -1.05 kcal/mol (destabilising).

IDENTITY

Variant	C360Y (p.Cysteine360Tyrosine)
DNA change	c.1079G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000374398
Amino acid change	Cysteine (C) → Tyrosine (Y)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 360	90.12 HIGH CONFIDENCE
Domain	Transmembrane helix 2
Position context	Inside Transmembrane helix 2 · position 360 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 360 sits in a transmembrane helix (Transmembrane helix 2). 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 thiol (cysteine — disulfide-capable, free -SH); 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

0.980am_class: **likely pathogenic** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-1.05** kcal/molDestabilising · Job
178092094476

PLDDT (ALPHAFOLD)

90.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/11/18 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	C360Y is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)
	<ul style="list-style-type: none">• Optic atrophy• Wolfram syndrome 1• Autosomal dominant nonsyndromic hearing loss 6• Type 2 diabetes mellitus• Wolfram-like syndrome• Cataract 41

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

$|\Delta\Delta G|=1.05 < 2$ kcal/mol (fold intact) + AlphaMissense 0.980 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution ($|\Delta\Delta G|=1.05$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.980. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.