

WFS1 C673G — Wolframin

Cysteine → Glycine at position 673. C-terminal ER-luminal (calcium binding. ClinVar Uncertain significance, AlphaMissense 0.994, DynaMut2 $\Delta\Delta G$ -1.31 kcal/mol (destabilising)).

IDENTITY

Variant	C673G (p.Cysteine673Glycine)
DNA change	c.2017T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003774536
Amino acid change	Cysteine (C) → Glycine (G)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 673	88.25 HIGH CONFIDENCE
Domain	C-terminal ER-luminal (calcium binding, calmodulin, chaperone)
Position context	C-terminal luminal domain · position 673 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

Position 673 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 thiol (cysteine — disulfide-capable, free -SH); the mutant is small/flexible (glycine — backbone flexibility, no sidechain). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.994am_class: **likely pathogenic** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-1.31** kcal/molDestabilising · Job
178092087351

PLDDT (ALPHAFOLD)

88.25

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2025/03/18 00:00
Inheritance	Autosomal recessive Wolfram syndrome 1 phenotype documented.
WFS1 variant landscape	C673G 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

$|\Delta\Delta G|=1.31 < 2$ kcal/mol (fold intact) + AlphaMissense 0.994 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution ($|\Delta\Delta G|=1.31$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.994. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.