MOLECULAR ATLAS · VARIANT CARD

WFS1 G656C — Wolframin

Glycine → Cysteine at position 656. C-terminal ER-lumenal (calcium binding. ClinVar Uncertain significance, AlphaMissense 0.946, DynaMut2 ΔΔG -0.47 kcal/mol (destabilising).

IDENTITY

Variant	G656C (p.Glycine656Cysteine)
DNA change	c.1966G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV004802688
Amino acid change	Glycine (G) → Cysteine (C)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 656	**48.88** BELOW IDR THRESHOLD
Domain	C-terminal ER-lumenal (calcium binding, calmodulin, chaperone)
Position context	C-terminal lumenal domain · position 656 projects into the ER lumen
IDR flag	YES — pLDDT 48.88 is below 50 threshold (route to Cat 5)

> Position 656 sits in the C-terminal lumenal 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 β1. The wild-type residue is small/flexible (glycine — backbone flexibility, no sidechain); 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	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.946	**-0.47** kcal/mol	**48.88**
am_class: **likely pathogenic** — threshold > 0.564	Destabilising · Job 178092141279	BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2025/05/24 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	G656C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no conditions catalogued)

RESEARCH PATH DECISION TREE

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ΔΔG < 2 + binding site affected → CATEGORY 3 — docking experiments ΔΔG 2–4 → CATEGORY
2 — pharmacological chaperones ΔΔG > 4 → CATEGORY 1 — gene therapy pLDDT < 50 →
CATEGORY 5 — IDR, experimental only Stable fold + functional site hit → CATEGORY 4 —
site-specific docking
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Category 5 — IDR Exclusion

pLDDT 48.88 is below 50; DynaMut2 result not trustworthy. Route to wet-lab.

Position sits in a low-confidence region. Computational stability estimates here are unreliable; this variant needs experimental characterization before any therapeutic strategy is set.
