

WFS1 M657I — Wolframin

Methionine → Isoleucine at position 657. C-terminal ER-luminal (calcium binding. ClinVar Uncertain significance, AlphaMissense 0.725, DynaMut2 $\Delta\Delta G$ +0.29 kcal/mol (stabilising).

IDENTITY

Variant	M657I (p.Methionine657Isoleucine)
DNA change	c.1971G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV004535980
Amino acid change	Methionine (M) → Isoleucine (I)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 657	51.97 CONFIDENT
Domain	C-terminal ER-luminal (calcium binding, calmodulin, chaperone)
Position context	C-terminal luminal domain · position 657 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

Position 657 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 hydrophobic sulfur (methionine); the mutant is medium hydrophobic (isoleucine — branched). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.725am_class: **likely pathogenic** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **0.29** kcal/mol

Stabilising · Job 178092152516

PLDDT (ALPHAFOLD)

51.97

confident

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2025/09/24 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	M657I 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

$|\Delta\Delta G|=0.29 < 2$ kcal/mol (fold intact) + AlphaMissense 0.725 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframín's fold survives this substitution ($|\Delta\Delta G|=0.29$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.725. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.