

WFS1 V709M — Wolframin

Valine → Methionine at position 709. C-terminal ER-luminal (calcium binding. ClinVar Uncertain significance, AlphaMissense 0.759, DynaMut2 $\Delta\Delta G$ -0.43 kcal/mol (destabilising).

IDENTITY

Variant	V709M (p.Valine709Methionine)
DNA change	c.2125G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001415749
Amino acid change	Valine (V) → Methionine (M)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 709	92.94 HIGH CONFIDENCE
Domain	C-terminal ER-luminal (calcium binding, calmodulin, chaperone)
Position context	C-terminal luminal domain · position 709 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

Position 709 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 small hydrophobic (valine — branched); the mutant is hydrophobic sulfur (methionine). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.759am_class: **likely pathogenic** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-0.43** kcal/molDestabilising · Job
178092120178

PLDDT (ALPHAFOLD)

92.94

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2024/12/14 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	V709M is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) <ul style="list-style-type: none"> Autosomal dominant nonsyndromic hearing loss 6 Type 2 diabetes mellitus Wolfram-like syndrome Cataract 41 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

$|\Delta\Delta G|=0.43 < 2$ kcal/mol (fold intact) + AlphaMissense 0.759 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution ($|\Delta\Delta G|=0.43$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.759. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.