

WFS1 F350C — Wolframin

Phenylalanine → Cysteine at position 350. Transmembrane helix 2. ClinVar Uncertain significance, AlphaMissense 0.860, DynaMut2 $\Delta\Delta G$ -1.26 kcal/mol (destabilising).

IDENTITY

Variant	F350C (p.Phenylalanine350Cysteine)
DNA change	c.1049T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003590682
Amino acid change	Phenylalanine (F) → Cysteine (C)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 350	93.38 HIGH CONFIDENCE
Domain	Transmembrane helix 2
Position context	Inside Transmembrane helix 2 · position 350 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 350 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 large aromatic hydrophobic (phenylalanine); 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

0.860

am_class: **likely pathogenic** —
threshold > 0.564

DYNAMUT2 $\Delta\Delta G$ **-1.26** kcal/mol

Destabilising · Job
178092112066

PLDDT (ALPHAFOLD)

93.38

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2024/01/24 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	F350C 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• Cataract 41• Wolfram syndrome 1• Wolfram-like syndrome• Type 2 diabetes mellitus

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

$|\Delta\Delta G|=1.26 < 2$ kcal/mol (fold intact) + AlphaMissense 0.860 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution ($|\Delta\Delta G|=1.26$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.860. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.