

WFS1 N325D — Wolframin

Asparagine → Aspartic acid at position 325. Transmembrane helix 1. ClinVar Uncertain significance, AlphaMissense 0.611, DynaMut2 $\Delta\Delta G$ +0.05 kcal/mol (stabilising).

IDENTITY

Variant	N325D (p.Asparagine325Aspartic acid)
DNA change	c.973A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002635787
Amino acid change	Asparagine (N) → Aspartic acid (D)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 325	75.75 HIGH CONFIDENCE
Domain	Transmembrane helix 1
Position context	Inside Transmembrane helix 1 · position 325 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

Position 325 sits in a transmembrane helix (Transmembrane helix 1). 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 polar amide (asparagine — H-bond donor/acceptor); the mutant is negatively charged (aspartate — carboxylate). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.611

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

DYNAMUT2 $\Delta\Delta G$ **0.05** kcal/mol

Stabilising · Job 178092131193

PLDDT (ALPHAFOLD)

75.75

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2023/04/10 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	N325D is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-related disorder

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

$|\Delta\Delta G|=0.05 < 2$ kcal/mol (fold intact) + AlphaMissense 0.611 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframín's fold survives this substitution ($|\Delta\Delta G|=0.05$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.611. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.