MOLECULAR ATLAS · VARIANT CARD

WFS1 G311D — Wolframin

Glycine → Aspartic acid at position 311. Transmembrane helix 1. ClinVar Uncertain significance, AlphaMissense 0.985, DynaMut2 ΔΔG -0.14 kcal/mol (destabilising).

IDENTITY

Variant	G311D (p.Glycine311Aspartic acid)
DNA change	c.932G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001477586
Amino acid change	Glycine (G) → Aspartic acid (D)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 311	**62.56** CONFIDENT
Domain	Transmembrane helix 1
Position context	Inside Transmembrane helix 1 · position 311 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

> Position 311 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 small/flexible (glycine — backbone flexibility, no sidechain); 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	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.985	**-0.14** kcal/mol	**62.56**
am_class: **likely pathogenic** — threshold > 0.564	Destabilising · Job 178092091142	confident

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CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2021/08/31 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	G311D 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 3/4 — Most Druggable

|ΔΔG|=0.14 < 2 kcal/mol (fold intact) + AlphaMissense 0.985 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.14 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.985. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.