MOLECULAR ATLAS · VARIANT CARD

WFS1 E199G — Wolframin

Glutamic acid → Glycine at position 199. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance, AlphaMissense 0.811, DynaMut2 ΔΔG -1.18 kcal/mol (destabilising).

IDENTITY

Variant	E199G (p.Glutamic acid199Glycine)
DNA change	c.596A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002631626
Amino acid change	Glutamic acid (E) → Glycine (G)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 199	**80.75** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic (intrinsically disordered)
Position context	N-terminal cytoplasmic (intrinsically disordered)
IDR flag	No — pLDDT well above 50 threshold

> Position 199 sits in N-terminal cytoplasmic (intrinsically disordered). The wild-type residue is negatively charged (glutamate — carboxylate); the mutant is small/flexible (glycine — backbone flexibility, no sidechain). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.811

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

DYNAMUT2 ΔΔG

-1.18 kcal/mol

Destabilising · Job 178092115425

PLDDT (ALPHAFOLD)

80.75

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2023/07/18 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	E199G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-related disorder

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|=1.18 < 2 kcal/mol (fold intact) + AlphaMissense 0.811 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=1.18 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.811. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
