MOLECULAR ATLAS · VARIANT CARD

WFS1 G831D — Wolframin

Glycine → Aspartate at position 831 in wolframin's C-terminal lumenal domain. ClinVar Conflicting. AlphaMissense 0.923, ΔΔG -0.85. Glycine-removal with charge introduction.

IDENTITY

Variant	G831D (p.Glycine831Aspartate)
DNA change	c.2492G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000004523
Amino acid change	Glycine (G) → Aspartate (D) — smallest amino acid replaced by negatively-charged carboxylate. Loss of backbone flexibility plus charge introduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 831	**78.12** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 831 (pLDDT 78).
IDR flag	No — pLDDT well above 50 threshold

Position 831 sits in the lumenal domain. Neighbors: ARG832 (2.5 Å — likely salt-bridge partner with new D831!), GLU830 (2.5 Å — adjacent existing carboxylate), LEU833 (4.7 Å), GLU694 (4.8 Å — long-range). Replacing G831 with aspartate creates a charge cluster: the new D831 carboxylate plus the existing E830, with R832 nearby as potential bridge. The local backbone flexibility is lost; the local electrostatic environment is transformed. The |ΔΔG| of 0.85 reflects substantial fold cost. AlphaMissense 0.923 confirms severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)

0.923

am_class: **LPath** — threshold > 0.564

-0.85 kcal/mol

Destabilising · Job 177992457119

78.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/02/04 00:00
Inheritance	Not specified.
WFS1 variant landscape	G831D is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific 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| = 0.85 — fold survives. AlphaMissense 0.923 confirms severe consequence.

Mechanism: glycine-removal plus charge introduction at the R832-E830 electrostatic environment. Therapeutic: site-directed at the 830-832 microregion.

G831D continues the glycine-removal class — universally pathogenic across the Atlas.