MOLECULAR ATLAS · VARIANT CARD

WFS1 G695D — Wolframin

Glycine → Aspartate at position 695 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic. AlphaMissense 0.954, DynaMut2 ΔΔG -1.77 kcal/mol (destabilising) — second-largest |ΔΔG| in this batch. A glycine-removal variant with substantial structural cost.

IDENTITY

Variant	G695D (p.Glycine695Aspartate)
DNA change	c.2084G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002798320
Amino acid change	Glycine (G) → Aspartate (D) — smallest amino acid replaced by small negatively-charged carboxylate-bearing residue. Loss of backbone flexibility plus charge introduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 695	**82.12** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 695 in the ER lumen (pLDDT 82).
IDR flag	No — pLDDT well above 50 threshold

Position 695 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places G695 within 5 Å of GLU694 (2.5 Å), HIS696 (2.5 Å — same H696 contacted by L829P at 3.9 Å), LEU829 (4.0 Å — partner of L829P!), ILE828 (4.0 Å), and LEU693 (4.5 Å). The G695-L829 contact at 4.0 Å is structurally significant — G695 sits in spatial contact with the L829P-perturbed microregion (133 sequence positions away). The wild-type glycine at 695 enables the backbone geometry that brings these distant residues into contact. Replacing glycine with aspartate at 695 introduces both backbone constraint and negative charge. The new D695 carboxylate competes with the existing E694 for local H-bonding. The L829 long-range contact is perturbed. The |ΔΔG| of 1.77 — the second-largest in this batch

and close to the Cat 2 threshold — reflects substantial structural cost. AlphaMissense's 0.954 confirms severe functional consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.954	**-1.77** kcal/mol	**82.12**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991930572	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2023/09/10 00:00
Inheritance	Inheritance not specified.
WFS1 variant landscape	G695D 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 (near Cat 2 boundary). |ΔΔG| = 1.77 — close to the Cat 2 threshold. AlphaMissense 0.954 confirms severe functional consequence.

Mechanism is glycine-removal at a position with long-range contact to L829 (133 sequence positions apart). Therapeutic strategy: stabilize the G695-L829 long-range geometry.

> G695D sits in long-range contact with L829P (Atlas card adjacent). Two Atlas variants 133 sequence positions apart converge on the same therapeutic target region through the folded geometry.
