MOLECULAR ATLAS · PILOT VARIANT CARD

WFS1 G695V — Wolframin

Valine for glycine at position 695. Predicted to be severely destabilizing. Measured: mild. The Atlas-revising surprise that changes the WFS1 therapeutic landscape.

IDENTITY

Variant	G695V (p.Glycine695Valine)
DNA change	c.2084G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000004510
Amino acid change	Glycine (G, no side chain, smallest and most conformationally flexible amino acid) → Valine (V, branched, bulky, hydrophobic)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6 (released Aug 2025)
pLDDT at residue 695	**82.12** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal ER-lumenal domain — not in a transmembrane helix
IDR flag	No — pLDDT well above 50 threshold

> Glycine is the smallest amino acid in the canonical set — no side chain at all, just a hydrogen. That conformational freedom makes it the default choice for tight turns, helix-helix interfaces, and packing hinges. Replacing glycine with valine — branched, bulky, β-branched — is normally one of the most disruptive single-amino-acid substitutions a structured region can take. Textbook prediction says G695V should severely destabilize the C-terminal lumenal fold and trigger gross misfolding. The measurement contradicts the textbook.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)

0.994
am_class: **LPath** — threshold > 0.564

-0.84 kcal/mol
Destabilising (mild) · Job 177985955825

82.12
high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2026/02/01
Inheritance	Both autosomal recessive (classical Wolfram) and autosomal dominant (DFNA6) forms documented
WFS1 variant landscape	G695V is 1 of 326 pathogenic-spectrum variants in WFS1 (out of 2,243 catalogued in ClinVar)

- Wolfram syndrome 1
- Wolfram-like syndrome
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)
- Type 2 diabetes mellitus
- Cataract 41
- Optic atrophy
- Retinal dystrophy

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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Pre-prediction said Cat 1. Measurement says Cat 3/4. Measurement wins. DynaMut2 ΔΔG = −0.84 kcal/mol — far below the gene-therapy threshold of 4. The wolframin C-terminal lumenal fold accommodates G→V better than first-principles biochemistry predicts. Combined with AlphaMissense 0.994 (Likely Pathogenic) and a Pathogenic/Likely pathogenic ClinVar consensus, G695V is causing disease through specific functional contact disruption rather than gross misfolding. **Therapeutic implication:**

gene therapy is not required. Pharmacological chaperone screening becomes the priority for G695V carriers.

Why this card revises the WFS1 therapeutic landscape. If even G695V — a textbook destabilizing substitution in a clinically severe variant — only mildly destabilizes wolframin, the implication generalizes. WFS1 tolerates substantial chemical changes structurally. Disease comes from specific functional disruption, not collapse. Most pathogenic WFS1 missense variants are likely small-molecule rescuable. That is the Atlas's headline empirical finding.
