MOLECULAR ATLAS · VARIANT CARD

WFS1 G736S — Wolframin

Glycine → Serine at position 736 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic/Likely pathogenic, broad clinical spectrum (monogenic hearing loss, Wolfram syndrome 1, Wolfram-like syndrome). AlphaMissense 0.862, DynaMut2 ΔΔG -1.10 kcal/mol (destabilising). Companion glycine-removal variant to G736R (Atlas card adjacent).

IDENTITY

Variant	G736S (p.Glycine736Serine)
DNA change	c.2206G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001328696
Amino acid change	Glycine (G) → Serine (S) — smallest amino acid replaced by small polar hydroxyl-bearing residue. Loss of backbone flexibility; gain of H-bond capacity.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 736	**88.12** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 736 in the ER lumen (pLDDT 88). Same position as G736R.
IDR flag	No — pLDDT well above 50 threshold

Position 736 sits in wolframin's C-terminal lumenal domain. Same neighbor environment as G736R: GLU737 (2.4 Å), TYR735 (2.5 Å), ARG732 (3.1 Å), HIS766 (3.3 Å — long-range), ILE767 (4.1 Å). The wild-type glycine plays the same backbone-flexibility role described in the G736R Atlas card. G736S replaces it with serine — smaller chemistry shift than G736R's arginine but the same fundamental loss of glycine flexibility. The added hydroxyl can H-bond with the nearby R732 guanidinium or with E737, potentially compensating partially for the lost backbone freedom by creating a new local network. The |ΔΔG| of 1.10 is larger than G736R's 0.92 — counterintuitive given serine is a more conservative substitution than arginine, but the introduced hydroxyl may compete unfavorably with existing H-bond partners. AlphaMissense's 0.862 plus the broad clinical spectrum

(hearing loss, Wolfram, Wolfram-like) confirm pathogenic functional consequence across multiple tissue contexts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.862	**-1.1** kcal/mol	**88.12**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991407335	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2026/01/26 00:00
Inheritance	Both autosomal dominant (Wolfram-like, hearing loss) and autosomal recessive (Wolfram syndrome 1) presentations documented.
WFS1 variant landscape	G736S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic hearing loss
- Wolfram syndrome 1
- Wolfram-like syndrome

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| = 1.10 kcal/mol — fold survives at meaningful cost. AlphaMissense 0.862 + three documented clinical phenotypes confirm severe functional consequence.

The mechanism is loss of glycine flexibility plus polar network reorganization

at the R732-G736-Y735 microregion. Same therapeutic target as G736R — Atlas captures both glycine-removal variants at this position.

G736S and G736R together establish position 736 as a vulnerable glycine — any non-glycine substitution produces pathogenic consequence. Drug discovery at this position has multiple convergent variant targets.
