

WFS1 G695S — Wolframin

Glycine → Serine at position 695 in lumenal domain. ClinVar Conflicting including Cataract 41 and DFNA6. AlphaMissense 0.906, $\Delta\Delta G$ -0.90. Same position as G695D (Atlas card adjacent).

IDENTITY

Variant	G695S (p.Glycine695Serine)
DNA change	c.2083G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002630486
Amino acid change	Glycine (G) → Serine (S) — smallest replaced by small polar hydroxyl. Loss of backbone flexibility, gain of H-bond.

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 (pLDDT 82). Same as G695D.
IDR flag	No — pLDDT well above 50 threshold

Position 695 same neighbors as G695D: GLU694 (2.5 Å), HIS696 (2.5 Å), LEU829 (4.0 Å — partner of L829P), ILE828 (4.0 Å), LEU693 (4.5 Å). G695S is the second substitution at position 695 (with G695D). The serine introduces polarity rather than charge, but both substitutions disrupt the wild-type glycine's backbone-flexibility role and perturb the long-range contact with L829. $|\Delta\Delta G|$ 0.90 + AlphaMissense 0.906 + Cataract 41 + DFNA6 confirm severe multi-tissue consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE 0.906	DYNAMUT2 $\Delta\Delta G$ -0.9 kcal/mol	PLDDT (ALPHAFOLD) 82.12
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am_class: **LPath** —
threshold > 0.564

Destabilising · Job
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high confidence

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2025/07/16 00:00

Inheritance

Both AD (DFNA6, Cataract 41) and AR
documented.

WFS1 variant landscape

G695S is 1 of ~326 pathogenic-spectrum
variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1
- Cataract 41
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

RESEARCH PATH DECISION TREE

$\Delta\Delta G < 2$ + binding site affected → CATEGORY 3 – docking experiments $\Delta\Delta G$
2–4 → CATEGORY 2 – pharmacological chaperones $\Delta\Delta G > 4$ → CATEGORY 1 –
gene therapy pLDDT < 50 → CATEGORY 5 – IDR, experimental only Stable
fold + functional site hit → CATEGORY 4 – site-specific docking

Category 3/4 — Most Druggable. $|\Delta\Delta G| = 0.90$ — fold survives.
AlphaMissense 0.906 + three phenotypes confirm severe consequence.

Mechanism: glycine removal + perturbed L829 long-range contact.
Therapeutic: same target as G695D.

G695S + G695D at same position; both connect to L829P long-range.
Position 695 is structurally critical for the L829-H696 microregion.