MOLECULAR ATLAS · VARIANT CARD

WFS1 G702S — Wolframin

Glycine → Serine at position 702 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic/Likely pathogenic, associated with optic atrophy and classical Wolfram syndrome 1. AlphaMissense 0.944, DynaMut2 ΔΔG -1.25 kcal/mol (destabilising). A glycine-removal variant near the V779 outlier region.

IDENTITY

Variant	G702S (p.Glycine702Serine)
DNA change	c.2104G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001373337
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 702	**88.75** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 702 in the ER lumen (pLDDT 89).
IDR flag	No — pLDDT well above 50 threshold

Position 702 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places G702 within 5 Å of ARG703 (2.4 Å), THR701 (2.5 Å), VAL779 (3.5 Å — same V779 as the V779G Cat 2 outlier), GLY780 (3.5 Å), and PRO782 (3.8 Å). The V779 contact is structurally significant: G702 sits in spatial proximity to the V779 region that V779G perturbs. The wild-type glycine at 702 provides backbone flexibility in a region densely packed with structurally constraining residues (R703 immediately downstream, V779/G780/P782 nearby). Replacing it with serine adds a small polar hydroxyl that the local environment cannot accommodate without rearrangement. The |ΔΔG| of 1.25 captures this — meaningful destabilization for a single substitution. AlphaMissense's 0.944 + optic atrophy + Wolfram syndrome 1 clinical associations confirm severe functional consequence. The mechanism

is loss of glycine flexibility plus perturbation of the V779 microregion that the Atlas already flags as a Cat 2 outlier site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.944	**-1.25** kcal/mol	**88.75**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991405251	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	Autosomal recessive Wolfram syndrome 1 phenotype documented; optic atrophy association consistent with the WFS1 spectrum.
WFS1 variant landscape	G702S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Optic atrophy
- Wolfram syndrome 1

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| = 1.25 kcal/mol — fold absorbs the substitution at meaningful cost. AlphaMissense 0.944 + optic atrophy + Wolfram 1 confirm severe functional consequence.

The mechanism is glycine-removal plus secondary disruption of the V779 microregion. Therapeutic strategy: site-directed at the G702-V779 contact

region. The V779G Atlas card identifies V779 as a Cat 2 outlier; G702S confirms the broader region is therapeutically significant.

G702S is the second Atlas variant directly contacting V779 (with the V779G Cat 2 outlier itself). The two variants together establish V779 as a structurally critical position in the lumenal domain — multiple Atlas variants converge there.
