MOLECULAR ATLAS · VARIANT CARD

WFS1 G562S — Wolframin

Glycine → Serine at position 562. Lumenal loop 4. ClinVar Uncertain significance, AlphaMissense 0.585, DynaMut2 ΔΔG -0.10 kcal/mol (destabilising).

IDENTITY

Variant	G562S (p.Glycine562Serine)
DNA change	c.1684G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001415009
Amino acid change	Glycine (G) → Serine (S)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 562	**82.56** HIGH CONFIDENCE
Domain	Lumenal loop 4
Position context	C-terminal lumenal domain · position 562 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

> Position 562 sits in the C-terminal lumenal domain (residues 653–869), wolframin's largest soluble region. This domain projects into the ER lumen and is implicated in calcium handling, ER stress sensing, and protein–protein interactions with ATF6 and Na+/K+ ATPase β1. The wild-type residue is small/flexible (glycine — backbone flexibility, no sidechain); the mutant is small polar (serine — hydroxyl). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.585

am_class: **likely pathogenic** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.1 kcal/mol

Destabilising · Job 178092156245

PLDDT (ALPHAFOLD)

82.56

high confidence

CLINICAL EVIDENCE

ClinVar classification	**UNCERTAIN SIGNIFICANCE**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2026/01/21 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	G562S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Inborn genetic diseases
- Autosomal dominant nonsyndromic hearing loss 6
- Type 2 diabetes mellitus
- Wolfram-like syndrome
- Cataract 41
- 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|=0.10 < 2 kcal/mol (fold intact) + AlphaMissense 0.585 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.10 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.585. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
