

WFS1 G576S — Wolframin

Glycine → Serine at position 576 inside TM8. ClinVar Conflicting including monogenic diabetes + WFS1 spectrum. AlphaMissense 0.15 (below threshold) — AM under-call. DynaMut2 $\Delta\Delta G$ -0.46.

IDENTITY

Variant	G576S (p.Glycine576Serine)
DNA change	c.1726G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000045439
Amino acid change	Glycine (G) → Serine (S) — smallest replaced by polar hydroxyl.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 576	83.75 HIGH CONFIDENCE
Domain	TM8 (563-583), helical transmembrane
Position context	TM8 (residues 563-583) · position 576 (pLDDT 84).
IDR flag	No — pLDDT well above 50 threshold

Position 576 in TM8. Neighbors: LEU577 (2.5 Å), ALA575 (2.5 Å — A575G partner!), ILE572 (3.5 Å). The 575-576 region — A575G + G576S adjacent. G576S removes glycine flexibility + adds polarity to TM8 bilayer environment. AM 0.15 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.145am_class: **LBen** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-0.46** kcal/

mol

Destabilising · Job
177992503415

PLDDT (ALPHAFOLD)

83.75

high confidence

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2026/02/02 00:00

Inheritance

Multi-phenotype.

WFS1 variant landscape

G576S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic diabetes
- WFS1-Related Spectrum Disorders

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 (AM under-call). $|\Delta\Delta G|$ 0.46.
AlphaMissense 0.15 below threshold but multi-phenotype confirms.

Mechanism: glycine removal + polarity in TM8. Therapeutic: same 575-576 region as A575G.

G576S + A575G — adjacent TM8 variants both pathogenic.