MOLECULAR ATLAS · VARIANT CARD

WFS1 G789S — Wolframin

Gly→Ser p789 IDR AM=0.07 ddg=-0.11 pLDDT=43. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	G789S (p.Glycine789Serine)
DNA change	c.2365G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001419650
Amino acid change	glycine flexibility lost

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 789	**43.34** BELOW IDR THRESHOLD
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal IDR
IDR flag	YES — pLDDT 43.34 is below 50 threshold (route to Cat 5)

Position analysis: SER790 (2.5 Å — partner of S790W/L), ASP788 (2.5 Å), ALA787 (4.5 Å — A787T). pLDDT 43 IDR boundary. Position 789 adjacent to multi-substitution 790. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.069

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.11 kcal/mol

Destabilising · Job 177992523646

PLDDT (ALPHAFOLD)

43.34

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/08/30 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	G789S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

RESEARCH PATH DECISION TREE

```
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
```

Cat 5 IDR — see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally identified. Therapeutic strategy: site-directed at contacts identified above, or wet-lab validation if pLDDT borderline/below 50.

IDR boundary near S790 cluster.
