

WFS1 G76V — Wolframin

Gly→Val p76 IDR AM=0.08 ddg=-1.11 pLDDT=26. ClinVar Conflicting evidence.
Atlas mechanism: see structural analysis.

IDENTITY

Variant	G76V (p.Glycine76Valine)
DNA change	c.227G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215375
Amino acid change	glycine flexibility lost

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 76	26.47 BELOW IDR THRESHOLD
Domain	N-terminal intrinsically disordered region (1-86)
Position context	N-terminal IDR
IDR flag	YES — pLDDT 26.47 is below 50 threshold (route to Cat 5)

Position analysis: THR77 (2.4 Å), ASP75 (2.5 Å), ALA74 (4.3 Å). pLDDT 26 deep IDR. Substantial $\Delta\Delta G$ but untrustworthy in this region. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.084am_class: **LBen** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-1.11** kcal/

mol

Destabilising · Job
177992520171

PLDDT (ALPHAFOLD)

26.47

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2026/01/05 00:00

Inheritance

Conflicting ClinVar classifications.

WFS1 variant landscape

G76V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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

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.

Deep IDR glycine removal.