MOLECULAR ATLAS · VARIANT CARD

WFS1 D267N — Wolframin

Asp→Asn p267 N-term AM=0.11 ddg=+0.77 pLDDT=31. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	D267N (p.Aspartate267Asparagine)
DNA change	c.799G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000166577
Amino acid change	charge loss, H-bond preserved

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 267	**31.11** BELOW IDR THRESHOLD
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic IDR-boundary
IDR flag	YES — pLDDT 31.11 is below 50 threshold (route to Cat 5)

> Position analysis: ASP268 (2.5 Å — adjacent existing D), GLN266 (2.5 Å), LEU265 (4.2 Å). pLDDT 31 deep IDR. DynaMut2 untrustworthy. The Atlas's neighbor extraction surfaces this variant's contacts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.109

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.77 kcal/mol

Stabilising · Job 177992511028

PLDDT (ALPHAFOLD)

31.11

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/21 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	D267N is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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 5 — see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally clear from neighbor analysis. Therapeutic strategy: site-directed at the contacts identified above.

deep IDR — wet-lab required.
