MOLECULAR ATLAS · VARIANT CARD

WFS1 D171N — Wolframin

Aspartate → Asparagine at position 171 in N-terminal cytoplasmic domain. ClinVar Conflicting. AlphaMissense 0.20 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.08 (neutral).

IDENTITY

Variant	D171N (p.Aspartate171Asparagine)
DNA change	c.511G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001330801
Amino acid change	Aspartate (D) → Asparagine (N) — carboxylate replaced by amide. Charge lost; H-bonding preserved.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 171	**85.19** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 171 (pLDDT 85).
IDR flag	No — pLDDT well above 50 threshold

> Position 171 in cytoplasmic domain. Neighbors: THR170 (2.5 Å), LEU172 (2.5 Å), ARG174 (3.8 Å — R174 partner of R177C cluster region). The R174-D171 likely salt bridge. D171N eliminates negative charge while preserving amide H-bond. R174 loses salt-bridge partner. ΔΔG ≈ 0; AM 0.20 under-call. ClinVar Conflicting with low evidence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.199

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.08 kcal/mol

PLDDT (ALPHAFOLD)

85.19

high confidence

	Destabilising · Job 177992498845	

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/10/24 00:00
Inheritance	Not specified.
WFS1 variant landscape	D171N 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
```

Category 4 — Stable Fold, Function Disrupted (AM under-call, low evidence). ΔΔG ≈ 0. AlphaMissense 0.20 below threshold. Limited clinical evidence.

Mechanism: loss of D171-R174 salt bridge. Therapeutic: same R174/R177 cluster microregion.

D171N targets the R174 microregion that R177C also disrupts.