MOLECULAR ATLAS · VARIANT CARD

WFS1 D379N — Wolframin

Asp→Asn p379 loop AM=0.10 ddg=-0.53 pLDDT=84. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	D379N (p.Aspartate379Asparagine)
DNA change	c.1135G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215355
Amino acid change	charge loss, H-bond preserved

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 379	**84.00** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: LEU380 (2.5 Å), THR378 (2.5 Å), ARG375 (3.7 Å — likely salt-bridge partner). Loop polar network disruption. The Atlas's neighbor extraction surfaces this variant's contacts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.098

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.53 kcal/mol

Destabilising · Job 177992517494

PLDDT (ALPHAFOLD)

84.00

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/11/15 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	D379N 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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Cat 3/4 — 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.

Loop charge-network disruption.
