MOLECULAR ATLAS · VARIANT CARD

WFS1 D339N — Wolframin

Aspartate → Asparagine at position 339 in connecting loop. ClinVar Conflicting including Wolfram. AlphaMissense 0.14 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.04 (neutral).

IDENTITY

Variant	D339N (p.Aspartate339Asparagine)
DNA change	c.1015G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215354
Amino acid change	Aspartate (D) → Asparagine (N) — charge loss; H-bonding preserved.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 339	**66.81** CONFIDENT
Domain	Connecting loop
Position context	Connecting loop · position 339 (pLDDT 67).
IDR flag	No — pLDDT well above 50 threshold

> Position 339 in connecting loop. Neighbors: ILE338 (2.5 Å), PHE340 (2.5 Å — TM2 start), ALA342 (3.8 Å — A342T position). D339N at boundary with TM2. The T337I-I338-D339-F340 region — adjacent to T337I Atlas card. AM 0.14 under-call; Wolfram confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.139

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.04 kcal/mol

Destabilising · Job 177992505559

PLDDT (ALPHAFOLD)

66.81

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/05/14 00:00
Inheritance	Wolfram syndrome 1.
WFS1 variant landscape	D339N is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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 4 — Stable Fold, Function Disrupted (AM under-call). ΔΔG ≈ 0. AlphaMissense 0.14 below threshold but Wolfram 1 confirms.

Mechanism: charge loss in 337-339 loop microregion. Therapeutic: same loop as T337I.

D339N + T337I in same loop region — A342T just downstream — multi-variant cluster.