MOLECULAR ATLAS · VARIANT CARD

WFS1 D367Y — Wolframin

Aspartate → Tyrosine at position 367 in a connecting loop. ClinVar Conflicting including Wolfram syndrome 1. AlphaMissense 0.685, ΔΔG +0.53 STABILISING.

IDENTITY

Variant	D367Y (p.Aspartate367Tyrosine)
DNA change	c.1099G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001810357
Amino acid change	Aspartate (D) → Tyrosine (Y) — small negatively-charged carboxylate replaced by large aromatic phenol. Charge loss + aromatic introduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 367	**79.50** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 367 (pLDDT 80).
IDR flag	No — pLDDT well above 50 threshold

Position 367 in connecting loop. Neighbors: GLN366 (2.5 Å), SER368 (2.5 Å), VAL364 (3.7 Å — near K363T), LYS363 (3.8 Å — partner of K363T!). The K363 contact is structurally significant: D367 wild-type likely salt-bridges with K363. Replacing D367 with tyrosine eliminates the salt-bridge potential. The variant fold stabilises (+0.53) because the aromatic ring packs into the local environment. AM 0.685 + Wolfram 1 confirm severe consequence. Mechanism is loss of D367-K363 salt bridge.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.685

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

0.53 kcal/mol

Stabilising · Job 177992465215

PLDDT (ALPHAFOLD)

79.50

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2023/02/13 00:00
Inheritance	Wolfram syndrome 1.
WFS1 variant landscape	D367Y 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. ΔΔG = +0.53 stabilising. AlphaMissense 0.685 + Wolfram 1 confirm severe consequence.

Mechanism: loss of D367-K363 salt bridge. Therapeutic: same K363 microregion as K363T.

D367Y + K363T are sister variants at the K363-D367 salt-bridge pair.