MOLECULAR ATLAS · VARIANT CARD

WFS1 K363T — Wolframin

Lysine → Threonine at position 363 in a connecting loop. ClinVar Likely pathogenic for Wolfram syndrome 1. AlphaMissense 0.874, DynaMut2 ΔΔG -0.43 kcal/mol (destabilising). Charge-loss variant adjacent to T361 (T361I Atlas card).

IDENTITY

Variant	K363T (p.Lysine363Threonine)
DNA change	c.1088A>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001327580
Amino acid change	Lysine (K) → Threonine (T) — large positively-charged amine replaced by small polar hydroxyl. Loss of charge and side-chain length.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 363	**85.50** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 363 in a loop region adjacent to T361 (pLDDT 86).
IDR flag	No — pLDDT well above 50 threshold

Position 363 sits in a connecting loop, two residues from T361 (T361I Atlas card). The AlphaFold model places K363 within 5 Å of LEU362 (2.5 Å), VAL364 (2.5 Å), CYS360 (3.6 Å), ILE359 (3.8 Å), and GLN366 (4.2 Å). The wild-type lysine at 363 is the partner residue identified in the T361I Atlas card — T361's hydroxyl was hypothesized to H-bond with K363's amine. K363T replaces lysine with threonine, which is precisely the residue that T361I introduced at the wild-type T position. The K363 amine is replaced by a hydroxyl. This means K363T and T361I together replace the wild-type T361-K363 H-bond pair (hydroxyl-amine) with a T361-T363 pair (hydroxyl-hydroxyl in the T361 variant; or the wild-type T plus T363 in the K363T variant). The geometry changes but H-bonding may persist. The |ΔΔG| of 0.43 reflects modest fold cost. AlphaMissense's 0.874 + Wolfram 1 confirm

severe functional consequence — the partner-recognition geometry depends on the precise wild-type chemistry, not just the H-bonding capacity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.874

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.43 kcal/mol

Destabilising · Job 177992006744

PLDDT (ALPHAFOLD)

85.50

high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	no assertion criteria provided
Last evaluated	2021/11/25 00:00
Inheritance	Wolfram syndrome 1 (AR) documented.
WFS1 variant landscape	K363T 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 3/4 — Most Druggable. |ΔΔG| = 0.43 — fold survives. AlphaMissense 0.874 + Wolfram 1 confirm severe functional consequence.

Mechanism is disruption of the T361-K363 H-bond pair. Therapeutic strategy: same microregion as T361I.

> K363T and T361I are sister variants at the same H-bond partner pair. Drug discovery in the T361-K363 microregion has two convergent variant targets.
