MOLECULAR ATLAS · VARIANT CARD

WFS1 A126T — Wolframin

Alanine → Threonine at position 126 in wolframin's N-terminal cytoplasmic domain. ClinVar Pathogenic/Likely pathogenic, associated with optic atrophy and Wolfram syndrome 1. AlphaMissense 0.878, DynaMut2 ΔΔG -1.76 kcal/mol (destabilising) — close to the Cat 2 threshold. The largest structural cost in this batch.

IDENTITY

Variant	A126T (p.Alanine126Threonine)
DNA change	c.376G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000372583
Amino acid change	Alanine (A) → Threonine (T) — small methyl-bearing hydrophobic replaced by small polar hydroxyl-bearing residue. Adds H-bond capacity.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 126	**93.00** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 126 in the cytosol with high AlphaFold confidence (pLDDT 93).
IDR flag	No — pLDDT well above 50 threshold

Position 126 sits in wolframin's N-terminal cytoplasmic domain. The AlphaFold model places A126 within 5 Å of THR125 (2.5 Å), VAL127 (2.5 Å), ASN122 (3.7 Å), SER123 (3.8 Å), and TYR110 (3.9 Å — longer-range). The local environment is polar-rich (T125, N122, S123) with a nearby aromatic (Y110) and an aliphatic neighbor (V127). The wild-type alanine contributes minimal side-chain mass. Replacing it with threonine introduces a polar hydroxyl into an already polar-rich environment — the new T126 hydroxyl competes for H-bonding partners with the existing T125, N122, and S123. The local H-bond network reorganizes. The |ΔΔG| of 1.76 is the largest in this batch and approaches the Cat 2 moderate-destabilization threshold. The fold absorbs the substitution but at meaningful cost. AlphaMissense's 0.878 plus

optic atrophy + Wolfram 1 clinical associations confirm pathogenic mechanism.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.878

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-1.76 kcal/mol

Destabilising · Job 177991406804

PLDDT (ALPHAFOLD)

93.00

high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2026/01/19 00:00
Inheritance	Wolfram syndrome 1 (AR) and optic atrophy documented.
WFS1 variant landscape	A126T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Optic atrophy
- 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 (high-confidence). |ΔΔG| = 1.76 kcal/mol — closest to the Cat 2 threshold in this batch but still fold-intact. AlphaMissense 0.878 + optic atrophy + Wolfram 1 confirm severe functional consequence.

The mechanism is reorganization of the T125-A126-N122-S123 polar network

through the introduced T126 hydroxyl. Therapeutic strategy: site-directed at the polar network — or pharmacological chaperone screening given the closer-to-Cat-2 stability cost.

A126T is the most structurally costly N-terminal cytoplasmic variant in this batch. The mechanism — polar network reorganization through a small additional H-bond donor — is mechanistically subtle but structurally substantial.
