MOLECULAR ATLAS · VARIANT CARD

WFS1 A179T — Wolframin

Alanine → Threonine at position 179. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance/Uncertain risk allele, AlphaMissense 0.934, DynaMut2 ΔΔG -2.09 kcal/mol (destabilising).

IDENTITY

Variant	A179T (p.Alanine179Threonine)
DNA change	c.535G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000229647
Amino acid change	Alanine (A) → Threonine (T)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 179	**88.56** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic (intrinsically disordered)
Position context	N-terminal cytoplasmic (intrinsically disordered)
IDR flag	No — pLDDT well above 50 threshold

> Position 179 sits in N-terminal cytoplasmic (intrinsically disordered). The wild-type residue is small/hydrophobic (alanine — methyl sidechain); the mutant is small polar (threonine — hydroxyl). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.934

am_class: **likely pathogenic** — threshold > 0.564

DYNAMUT2 ΔΔG

-2.09 kcal/mol

Destabilising · Job 178092143728

PLDDT (ALPHAFOLD)

88.56

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE/UNCERTAIN RISK ALLELE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2026/02/23 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	A179T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Cataract 41
- Autosomal dominant nonsyndromic hearing loss 6
- Type 2 diabetes mellitus
- Wolfram syndrome 1
- Wolfram-like syndrome
- Inborn genetic diseases

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 2 — Moderately Destabilizing**
>
> |ΔΔG|=2.09 in the 2–4 range. Pharmacological chaperone candidate.
