

WFS1 A133T — Wolframin

Alanine → Threonine at position 133 in N-terminal cytoplasmic domain. ClinVar Conflicting including Wolfram-like + Cataract 41. AlphaMissense 0.878, $\Delta\Delta G$ -1.83 (close to Cat 2 boundary).

IDENTITY

Variant	A133T (p.Alanine133Threonine)
DNA change	c.397G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001331467
Amino acid change	Alanine (A) → Threonine (T) — small methyl-bearing hydrophobic replaced by small polar hydroxyl.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 133	92.00 HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 133 (pLDDT 92).
IDR flag	No — pLDDT well above 50 threshold

Position 133 sits in cytoplasmic domain. Neighbors: LEU132 (2.5 Å), ALA134 (2.5 Å), GLN103 (3.5 Å — long-range), LEU130 (3.8 Å). Adjacent to A126T microregion (A126T at 4.5 Å away in sequence; both in same broader cytoplasmic pocket). Replacing A133 with threonine introduces polarity into a hydrophobic cytoplasmic pocket. The Q103 long-range contact at 3.5 Å suggests the variant T133 hydroxyl could H-bond with Q103, but the geometric cost is substantial. $|\Delta\Delta G|$ 1.83 close to Cat 2 threshold reflects this. AlphaMissense 0.878 + Wolfram-like + Cataract 41 confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

DYNAMUT2 $\Delta\Delta G$

PLDDT (ALPHAFOLD)

0.878

am_class: **LPath** —
threshold > 0.564

-1.83 kcal/

mol
Destabilising · Job
177992460997

92.00

high confidence

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2025/11/05 00:00

Inheritance

Wolfram-like + Cataract 41 documented.

WFS1 variant landscape

A133T is 1 of ~326 pathogenic-spectrum
variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram-like syndrome
- Cataract 41

RESEARCH PATH DECISION TREE

$\Delta\Delta G < 2$ + binding site affected → CATEGORY 3 – docking experiments $\Delta\Delta G$
2–4 → CATEGORY 2 – pharmacological chaperones $\Delta\Delta G > 4$ → CATEGORY 1 –
gene therapy pLDDT < 50 → CATEGORY 5 – IDR, experimental only Stable
fold + functional site hit → CATEGORY 4 – site-specific docking

Category 3/4 — Most Druggable (near Cat 2 boundary). $|\Delta\Delta G| = 1.83$
— closest to Cat 2 threshold in this batch. AlphaMissense 0.878 confirms
severe consequence.

Mechanism: polarity introduction into a hydrophobic cytoplasmic pocket.
Therapeutic: same N-terminal microregion as A126T (close in sequence and
structure).

A133T + A126T together establish the 126-133 cytoplasmic microregion as a
multi-variant target.

