

WFS1 I296T — Wolframin

Isoleucine → Threonine at position 296. N-terminal cytoplasmic (intrinsically disordered). ClinVar Uncertain significance, AlphaMissense 0.866, DynaMut2 $\Delta\Delta G$ -0.85 kcal/mol (destabilising).

IDENTITY

Variant	I296T (p.Isoleucine296Threonine)
DNA change	c.887T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002781305
Amino acid change	Isoleucine (I) → Threonine (T)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 296	67.19 CONFIDENT
Domain	N-terminal cytoplasmic (intrinsically disordered)
Position context	N-terminal cytoplasmic (intrinsically disordered)
IDR flag	No — pLDDT well above 50 threshold

Position 296 sits in N-terminal cytoplasmic (intrinsically disordered). The wild-type residue is medium hydrophobic (isoleucine — branched); 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

0.866am_class: **likely pathogenic** — threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-0.85** kcal/mol

Destabilising · Job 178092146285

PLDDT (ALPHAFOLD)

67.19

confident

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2024/01/14 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	I296T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) <ul style="list-style-type: none"> • Cataract 41 • Wolfram syndrome 1 • Wolfram-like syndrome • Autosomal dominant nonsyndromic hearing loss 6 • Type 2 diabetes mellitus

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

$|\Delta\Delta G|=0.85 < 2$ kcal/mol (fold intact) + AlphaMissense 0.866 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution ($|\Delta\Delta G|=0.85$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.866. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.