

WFS1 T455K — Wolframin

Threonine → Lysine at position 455. Cytoplasmic loop 3. ClinVar Uncertain significance, AlphaMissense 0.895, DynaMut2 $\Delta\Delta G$ -0.52 kcal/mol (destabilising).

IDENTITY

Variant	T455K (p.Threonine455Lysine)
DNA change	c.1364C>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002053650
Amino acid change	Threonine (T) → Lysine (K)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 455	83.62 HIGH CONFIDENCE
Domain	Cytoplasmic loop 3
Position context	Loop region · position 455 sits between transmembrane segments, solvent-accessible
IDR flag	No — pLDDT well above 50 threshold

Position 455 sits in a connecting loop between transmembrane helices. Loop residues are typically solvent-exposed and often contribute to interhelical contacts or serve as recognition sites for binding partners. The wild-type residue is small polar (threonine — hydroxyl); the mutant is positively charged (lysine — primary amine). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.895am_class: **likely pathogenic** — threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-0.52** kcal/molDestabilising · Job
178092108319

PLDDT (ALPHAFOLD)

83.62

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2022/04/10 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	T455K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) <ul style="list-style-type: none">(no conditions catalogued)

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

$|\Delta\Delta G|=0.52 < 2$ kcal/mol (fold intact) + AlphaMissense 0.895 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframins fold survives this substitution ($|\Delta\Delta G|=0.52$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.895. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.