MOLECULAR ATLAS · VARIANT CARD

WFS1 P504T — Wolframin

Proline → Threonine at position 504. Transmembrane helix 7. ClinVar Uncertain significance, AlphaMissense 0.758, DynaMut2 ΔΔG -1.31 kcal/mol (destabilising).

IDENTITY

Variant	P504T (p.Proline504Threonine)
DNA change	c.1510C>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000425325
Amino acid change	Proline (P) → Threonine (T)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 504	**82.88** HIGH CONFIDENCE
Domain	Transmembrane helix 7
Position context	Inside Transmembrane helix 7 · position 504 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

> Position 504 sits in a transmembrane helix (Transmembrane helix 7). Wolframin has eleven such helices anchoring it in the ER membrane; substitutions inside the bilayer-embedded segments can disrupt helix packing, lipid contacts, and the overall ER topology of the protein. The wild-type residue is rigid/helix-breaking (proline — kinks backbone); 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

0.758

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

DYNAMUT2 ΔΔG

-1.31 kcal/mol

Destabilising · Job 178092120012

PLDDT (ALPHAFOLD)

82.88

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2016/11/01 00:00
Inheritance	Autosomal recessive Wolfram syndrome 1 phenotype documented.
WFS1 variant landscape	P504T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- 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

|ΔΔG|=1.31 < 2 kcal/mol (fold intact) + AlphaMissense 0.758 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=1.31 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.758. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
