

WFS1 P52T — Wolframin

Pro→Thr p52 IDR AM=0.07 ddg=-0.24 pLDDT=44. ClinVar Conflicting evidence.
Atlas mechanism: see structural analysis.

IDENTITY

Variant	P52T (p.Proline52Threonine)
DNA change	c.154C>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000593883
Amino acid change	proline removal

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 52	44.25 BELOW IDR THRESHOLD
Domain	N-terminal intrinsically disordered region (1-86)
Position context	N-terminal IDR boundary
IDR flag	YES — pLDDT 44.25 is below 50 threshold (route to Cat 5)

Position analysis: GLY53 (2.5 Å), GLY51 (2.5 Å — Gly-Pro-Gly motif!). pLDDT 44 IDR boundary. Sparse neighbors. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.068am_class: **LBen** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-0.24** kcal/

mol

Destabilising · Job
177992523195

PLDDT (ALPHAFOLD)

44.25

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	CONFLICTING CLASSIFICATIONS OF PATHOGENICITY
Review status	criteria provided, conflicting classifications
Last evaluated	2026/02/17 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	P52T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

RESEARCH PATH DECISION TREE

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

Cat 5 IDR — see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally identified. Therapeutic strategy: site-directed at contacts identified above, or wet-lab validation if pLDDT borderline/below 50.

IDR-boundary proline-removal.