MOLECULAR ATLAS · VARIANT CARD

WFS1 L382P — Wolframin

Leucine → Proline at position 382 in a connecting loop. ClinVar Conflicting including Wolfram-like syndrome. AlphaMissense 0.922, ΔΔG -0.40 (mild destabilising). Proline-introduction in a loop region.

IDENTITY

Variant	L382P (p.Leucine382Proline)
DNA change	c.1145T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001699545
Amino acid change	Leucine (L) → Proline (P) — branched aliphatic hydrophobic replaced by rigid helix-breaking residue.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 382	**85.31** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 382 (pLDDT 85).
IDR flag	No — pLDDT well above 50 threshold

> Position 382 sits in a connecting loop. Neighbors: ARG383 (2.5 Å — partner of R383H — not yet in Atlas), LEU381 (2.5 Å), GLU385 (3.6 Å — partner of E385K), THR378 (3.8 Å). Replacing L382 with proline introduces a backbone kink in the loop. The R383 partner residue (with E385 forming a likely salt-bridge or H-bond network) experiences perturbed geometry. The |ΔΔG| of 0.40 reflects modest fold cost; AlphaMissense 0.922 + Wolfram-like confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.922	**-0.4** kcal/mol	**85.31** high confidence

am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992457478	

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2024/10/17 00:00
Inheritance	Wolfram-like syndrome documented.
WFS1 variant landscape	L382P is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram-like syndrome

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| = 0.40 — fold survives. AlphaMissense 0.922 confirms severe consequence.

Mechanism: proline-induced backbone kink in the R383-E385 microregion. Therapeutic: same loop region (E385K adjacent).

L382P + E385K at adjacent positions — multi-variant target cluster in the 382-385 loop.

RareResearch.AI · WFS1 Molecular Atlas · Generated by wolfram-variant-card skill *Every assumption documented.*