

Variant: NM_000546.5(TP53):c.541C>A (p.Arg181Ser)

Version: 1.1

CA10580940 [↗](#)

230764 (ClinVar) [↗](#)

Gene: TP53 ([HGNC:7157](#))
Condition: Li-Fraumeni syndrome ([MONDO:0018875](#))
Inheritance Mode: Autosomal dominant inheritance
UUID: dc88e22c-bbbf-4aeb-9c2a-0e3babeaaeed
Approved on: 2025/3/4
Published on: 2025/6/23

HGVS expressions

NM_000546.5(TP53):c.541C>A (p.Arg181Ser)
NM_000546.5:c.541C>A
NC_000017.11:g.7675071G>T
CM000679.2:g.7675071G>T
NC_000017.10:g.7578389G>T
CM000679.1:g.7578389G>T
NC_000017.9:g.7519114G>T
NG_017013.2:g.17480C>A
ENST00000503591.2:c.541C>A
ENST00000508793.6:c.541C>A
ENST00000509690.6:c.145C>A
ENST00000514944.6:c.262C>A
ENST00000604348.6:c.520C>A
ENST00000269305.9:c.541C>A
ENST00000269305.8:c.541C>A
ENST00000359597.8:c.541C>A
ENST00000413465.6:c.541C>A
ENST00000420246.6:c.541C>A
ENST00000445888.6:c.541C>A
ENST00000455263.6:c.541C>A
ENST00000504290.5:c.145C>A
ENST00000504937.5:c.145C>A
ENST00000505014.5:n.797C>A
ENST00000509690.5:c.145C>A
ENST00000510385.5:c.145C>A
ENST00000514944.5:c.262C>A
ENST00000574684.1:n.49C>A
ENST00000610292.4:c.424C>A
ENST00000610538.4:c.424C>A
ENST00000610623.4:c.64C>A
ENST00000615910.4:c.508C>A
ENST00000617185.4:c.541C>A
ENST00000618944.4:c.64C>A
ENST00000619186.4:c.64C>A
ENST00000619485.4:c.424C>A
ENST00000620739.4:c.424C>A
ENST00000622645.4:c.424C>A

	ENST00000635293.1:c.424C>A
	NM_001126112.2:c.541C>A
	NM_001126113.2:c.541C>A
	NM_001126114.2:c.541C>A
	NM_001126115.1:c.145C>A
	NM_001126116.1:c.145C>A
	NM_001126117.1:c.145C>A
	NM_001126118.1:c.424C>A
	NM_001276695.1:c.424C>A
	NM_001276696.1:c.424C>A
	NM_001276697.1:c.64C>A
	NM_001276698.1:c.64C>A
	NM_001276699.1:c.64C>A
	NM_001276760.1:c.424C>A
	NM_001276761.1:c.424C>A
	NM_001276695.2:c.424C>A
	NM_001276696.2:c.424C>A
	NM_001276697.2:c.64C>A
	NM_001276698.2:c.64C>A
	NM_001276699.2:c.64C>A
	NM_001276760.2:c.424C>A
	NM_001276761.2:c.424C>A
	NM_000546.6:c.541C>A
	NM_001126112.3:c.541C>A
	NM_001126113.3:c.541C>A
	NM_001126114.3:c.541C>A
	NM_001126115.2:c.145C>A
	NM_001126116.2:c.145C>A
	NM_001126117.2:c.145C>A
	NM_001126118.2:c.424C>A
	NM_001276695.3:c.424C>A
	NM_001276696.3:c.424C>A
	NM_001276697.3:c.64C>A
	NM_001276698.3:c.64C>A
	NM_001276699.3:c.64C>A
	NM_001276760.3:c.424C>A
	NM_001276761.3:c.424C>A

Uncertain Significance

Met criteria codes 4

- BS2_Supporting
- PP3_Moderate
- BS3_Supporting
- PM2_Supporting

Not Met criteria codes 11

- PM1
- PM6
- BS1
- BS4
- PS1
- PS2
- PS3
- PS4
- BP4
- BA1
- PP1

Evidence Links 0

Expert Panel

TP53 VCEP

Criteria Specification Information

[Criteria Specification:](#) ClinGen TP53 Expert Panel
Specifications to the ACMG/AMP Variant Interpretation
Guidelines for TP53 Version 2.3.0

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)

TP53 VCEP

The NM_000546.6:c.541C>A variant in TP53 is a missense variant predicted to cause substitution of arginine by serine at amino acid 181 (p.Arg181Ser). This variant has been observed in 3 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Supporting; Ambry SCV000274425.4). This variant received a total of 0.5 points across 1 family meeting Chompret criteria and does not meet criteria for PS4 (PS4 not met; IARC database). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation, and retained growth suppression activity indicating that this variant does not impact protein function (BS3_Supporting; PMIDs: 12826609, 29979965, 30224644). Computational predictor scores (BayesDel = 0.204; Align GVGD = Class C65) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate). In summary, this variant meets the criteria to be classified as a variant of unknown significance for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2_supporting, PM2_supporting, BS3_supporting, PP3_moderate (Bayesian Points: 1; VCEP specifications version 2.3).

Met criteria codes

BS2_Supporting			This variant has been observed in 3 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Supporting; Ambry SCV000274425.4).
PP3_Moderate			Computational predictor scores (BayesDel = 0.204; Align GVGD = Class C65) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate).
BS3_Supporting			In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation, and retained growth suppression activity indicating that this variant does not impact protein function (BS3_Supporting; PMIDs: 12826609, 29979965, 30224644).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PM1			This variant does not reside within a region of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PM1 not met).
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			This variant received a total of 0.5 points across 1 family meeting Chompret criteria and does not meet criteria for PS4 (PS4 not met; IARC database).
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 	
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