The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000546.5(TP53):c.221C>T (p.Ala74Val)

Version: 1.1

CA000077

141547 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: ad0ddb25-8464-4d3f-b3c7-c54eb5535e21
Approved on: 2025-01-16
Published on: 2025-01-16

HGVS expressions

NM_000546.5:c.221C>T
NM_000546.5(TP53):c.221C>T (p.Ala74Val)
NC_000017.11:g.7676148G>A
CM000679.2:g.7676148G>A
NC_000017.10:g.7579466G>A
CM000679.1:g.7579466G>A
NC_000017.9:g.7520191G>A
NG_017013.2:g.16403C>T
ENST00000503591.2:c.221C>T
ENST00000508793.6:c.221C>T
ENST00000509690.6:c.-21-912C>T
ENST00000514944.6:c.96+234C>T
ENST00000604348.6:c.221C>T
ENST00000269305.9:c.221C>T
ENST00000269305.8:c.221C>T
ENST00000359597.8:c.221C>T
ENST00000413465.6:c.221C>T
ENST00000420246.6:c.221C>T
ENST00000445888.6:c.221C>T
ENST00000455263.6:c.221C>T
ENST00000503591.1:c.221C>T
ENST00000505014.5:n.477C>T
ENST00000508793.5:c.221C>T
ENST00000509690.5:c.-21-912C>T
ENST00000514944.5:c.96+234C>T
ENST00000604348.5:c.221C>T
ENST00000610292.4:c.104C>T
ENST00000610538.4:c.104C>T
ENST00000615910.4:c.221C>T
ENST00000617185.4:c.221C>T
ENST00000619485.4:c.104C>T
ENST00000620739.4:c.104C>T
ENST00000622645.4:c.104C>T
ENST00000635293.1:c.104C>T
NM_001126112.2:c.221C>T
NM_001126113.2:c.221C>T
NM_001126114.2:c.221C>T

NM_001126118.1:c.104C>T
NM_001276695.1:c.104C>T
NM_001276696.1:c.104C>T
NM_001276760.1:c.104C>T
NM_001276761.1:c.104C>T
NM_001276695.2:c.104C>T
NM_001276696.2:c.104C>T
NM_001276760.2:c.104C>T
NM_001276761.2:c.104C>T
NM_000546.6:c.221C>T
NM_001126112.3:c.221C>T
NM_001126113.3:c.221C>T
NM_001126114.3:c.221C>T
NM_001126118.2:c.104C>T
NM_001276695.3:c.104C>T
NM_001276696.3:c.104C>T
NM_001276760.3:c.104C>T
NM_001276761.3:c.104C>T

Likely Benign

Met criteria codes 4

PM2_Supporting BS2_Supporting BS3 BP4

Not Met criteria codes 18

BS1 BS4 BP3 BP2 PVS1 BP7 PS1 PS2 PS3 PS4 BA1 PP1 PP3 PP4 PM6 PM1 PM5 PM4

Evidence Links 3

Expert Panel

TP53 VCEP

Criteria Specification Information

Criteria Specification: *ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.1.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.221C>T variant in TP53 is a missense variant predicted to cause substitution of alanine by valine at amino acid 74 (p.Ala74Val). This variant has been observed in 2-3 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; Internal lab contributors). This variant has an allele frequency of 0.000006782 (8/1179650 alleles) in the European (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 29979965, 30224644). Computational predictor scores (BayesDel = -0.2135; Align GVGD Class C0) are below the recommended thresholds (BayesDel ≤ -0.008 and an Align GVGD Class ≤ 55), evidence that does not predict a damaging effect on TP53 via protein change. SpliceAI predicts that the variant has no impact on splicing. (BP4_Moderate). In summary, this variant meets the criteria to be classified as likely benign for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2_Supporting, BS3, BP4_Moderate, PM2_Supporting. (Bayesian Points: -6; VCEP specifications version 2.1; 1/16/2025).

Met criteria codes

PM2_Supporting	✔	This variant has an allele frequency of 0.000006782 (8/1179650 alleles) in the European (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
BS2_Supporting	✔	This variant has been observed in 2-3 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; Internal lab contributors).
BS3	✔	In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 29979965, 30224644). Giacomelli A549_p53NULL_Etoposide_Z-score (LOF <=-0.21) = 0.700463717 Giacomelli A549_p53WT_Nutlin-3_Z-score (DN=>0.61) = -0.214822468 PubMed:30224644 Kato transactivation functional, 82.8% PubMed:12826609 N/A PubMed:29979965
BP4	✔	BP4_MODERATE Computational predictor scores (BayesDel = -0.2135; Align GVGD Class C0) are below the recommended thresholds (BayesDel ≤ -0.008 and an Align GVGD Class ≤ 55), evidence that does not predict a damaging effect on TP53 via protein change. SpliceAI predicts that the variant has no impact on splicing. (BP4_Moderate).

Not Met criteria codes

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
BP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	ℹ	✖	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).
PM5	ℹ	✖	2 different missense variants (p.Ala74Gly, p.Ala74Ser) in the same codon have been reported (ClinVar Variation IDs: 1787901, 1361776). However, the variants have not yet been curated to determine if they would be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP’s specifications (PM5 not evaluated).
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 2 of 2 rows