

Variant: NM_001126112.2(TP53):c.188C>T (p.Ala63Val)

Version: 2.0

CA000063 [↗](#)

182922 (ClinVar) [↗](#)

Gene: TP53 ([HGNC:7157](#))

Condition: Li-Fraumeni syndrome ([MONDO:0018875](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: ef9d90c6-8b7a-4989-9f0f-7bd7f52113b0

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HGVS expressions

NM_001126112.2:c.188C>T

NM_001126112.2(TP53):c.188C>T (p.Ala63Val)

NC_000017.11:g.7676181G>A

CM000679.2:g.7676181G>A

NC_000017.10:g.7579499G>A

CM000679.1:g.7579499G>A

NC_000017.9:g.7520224G>A

NG_017013.2:g.16370C>T

ENST00000503591.2:c.188C>T

ENST00000508793.6:c.188C>T

ENST00000509690.6:c.-21-945C>T

ENST00000514944.6:c.96+201C>T

ENST00000604348.6:c.188C>T

ENST00000269305.9:c.188C>T

ENST00000269305.8:c.188C>T

ENST00000359597.8:c.188C>T

ENST00000413465.6:c.188C>T

ENST00000420246.6:c.188C>T

ENST00000445888.6:c.188C>T

ENST00000455263.6:c.188C>T

ENST00000503591.1:c.188C>T

ENST00000505014.5:n.444C>T

ENST00000508793.5:c.188C>T

ENST00000509690.5:c.-21-945C>T

ENST00000514944.5:c.96+201C>T

ENST00000604348.5:c.188C>T

ENST00000610292.4:c.71C>T

ENST00000610538.4:c.71C>T

ENST00000615910.4:c.188C>T

ENST00000617185.4:c.188C>T

ENST00000619485.4:c.71C>T

ENST00000620739.4:c.71C>T

ENST00000622645.4:c.71C>T

ENST00000635293.1:c.71C>T

NM_000546.5:c.188C>T

NM_001126113.2:c.188C>T

NM_001126114.2:c.188C>T

NM_001126118.1:c.71C>T
NM_001276695.1:c.71C>T
NM_001276696.1:c.71C>T
NM_001276760.1:c.71C>T
NM_001276761.1:c.71C>T
NM_001276695.2:c.71C>T
NM_001276696.2:c.71C>T
NM_001276760.2:c.71C>T
NM_001276761.2:c.71C>T
NM_000546.6:c.188C>T
NM_001126112.3:c.188C>T
NM_001126113.3:c.188C>T
NM_001126114.3:c.188C>T
NM_001126118.2:c.71C>T
NM_001276695.3:c.71C>T
NM_001276696.3:c.71C>T
NM_001276760.3:c.71C>T
NM_001276761.3:c.71C>T

Benign

Met criteria codes 3

BS3 BS2_Supporting BP4

Not Met criteria codes 13

PM1 PM5 PM2 BS1 BS4
PS1 PS2 PS3 PS4 BA1 PP1
PP3 PP4

Evidence Links 2

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.188C>T variant in TP53 is a missense variant predicted to cause substitution of Alanine by Valine at amino acid 63 (p.Ala63Val). 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 contributor: Invitae). 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 = -0.099; 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 Benign for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2_Supporting, BS3, BP4_Moderate. (Bayesian Points: -7; VCEP specifications version 2.1; 1/16/2025).

Met criteria codes

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).

Functional at 83% [PubMed:12826609](#)
No LOF [PubMed:30224644](#)

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 contributor: Invitae).
BP4			BP4_MODERATE Computational predictor scores (BayesDel = -0.099; Align GVGD Class C0) are below the recommended thresholds (BayesDel $\leq$ -0.008 and an Align GVGD Class $\leq$ 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

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).
PM5			2 different missense variants (p.Ala63Gly, p.Ala63Thr) in the same codon have been reported (ClinVar Variation IDs: 229693, 231015). However, these variants have not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP’s specifications (PM5 not met).
PM2			The highest population minor allele frequency in gnomAD v4.1.0 is 0.00004456 (2/44880 alleles) in the East Asian population (PM2, BS1, and BA1 are not met).
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			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
PP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
		
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