

Variant: *NM_000546.5(TP53):c.217G>A (p.Val73Met)*

Version: 3.0

CA000075 [↗](#)

142386 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: f34e83bc-68f7-4351-8dc9-2d94aa0ddeac

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HGVS expressions

NM_000546.5(TP53):c.217G>A (p.Val73Met)

NM_000546.5:c.217G>A

NC_000017.11:g.7676152C>T

CM000679.2:g.7676152C>T

NC_000017.10:g.7579470C>T

CM000679.1:g.7579470C>T

NC_000017.9:g.7520195C>T

NG_017013.2:g.16399G>A

ENST00000503591.2:c.217G>A

ENST00000508793.6:c.217G>A

ENST00000509690.6:c.-21-916G>A

ENST00000514944.6:c.96+230G>A

ENST00000604348.6:c.217G>A

ENST00000269305.9:c.217G>A

ENST00000269305.8:c.217G>A

ENST00000359597.8:c.217G>A

ENST00000413465.6:c.217G>A

ENST00000420246.6:c.217G>A

ENST00000445888.6:c.217G>A

ENST00000455263.6:c.217G>A

ENST00000503591.1:c.217G>A

ENST00000505014.5:n.473G>A

ENST00000508793.5:c.217G>A

ENST00000509690.5:c.-21-916G>A

ENST00000514944.5:c.96+230G>A

ENST00000604348.5:c.217G>A

ENST00000610292.4:c.100G>A

ENST00000610538.4:c.100G>A

ENST00000615910.4:c.217G>A

ENST00000617185.4:c.217G>A

ENST00000619485.4:c.100G>A

ENST00000620739.4:c.100G>A

ENST00000622645.4:c.100G>A

ENST00000635293.1:c.100G>A

NM_001126112.2:c.217G>A

NM_001126113.2:c.217G>A

NM_001126114.2:c.217G>A

NM_001126118.1:c.100G>A
NM_001276695.1:c.100G>A
NM_001276696.1:c.100G>A
NM_001276760.1:c.100G>A
NM_001276761.1:c.100G>A
NM_001276695.2:c.100G>A
NM_001276696.2:c.100G>A
NM_001276760.2:c.100G>A
NM_001276761.2:c.100G>A
NM_000546.6:c.217G>A
NM_001126112.3:c.217G>A
NM_001126113.3:c.217G>A
NM_001126114.3:c.217G>A
NM_001126118.2:c.100G>A
NM_001276695.3:c.100G>A
NM_001276696.3:c.100G>A
NM_001276760.3:c.100G>A
NM_001276761.3:c.100G>A

Benign

Met criteria codes 3

BS2 BS3 BP4

Not Met criteria codes 8

PM1 PM5 PM2 BS1 PS1
PS3 BA1 PP3

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 2.0.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.217G>A variant in TP53 is a missense variant predicted to cause substitution of valine by methionine at amino acid 73 (p.Val73Met). This variant has been observed in 4-7 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_Moderate; ClinVar SCV: SCV000186461.7). The highest population minor allele frequency in gnomAD v2.1.1 (non-cancer) is 0.001037 (11/10608 alleles) in European (Finnish) population (PM2, BS1, and BA1 are not met). 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 (PMIDs: 12826609, 29979965, 30224644) (BS3). Computational predictor scores (BayesDel = -0.1673; 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: BS3, BS2_Moderate, BP4_Moderate. (Bayesian Points: -8; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

BS2			BS2_MODERATE APPLIED This variant has been observed in 4-7 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_Moderate; ClinVar SCV: SCV000186461.7).
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 (PMIDs: 12826609, 29979965, 30224644) (BS3)
BP4			BP4_MODERATE APPLIED Computational predictor scores (BayesDel = -0.1673; 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			Another missense variant (c.218T>C, p.Val73Ala) in the same codon have been reported (ClinVar Variation ID: 2168377). 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 met).
PM2			The highest population minor allele frequency in gnomAD v41.0 is 0.00004457 (2/44878 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
PS1			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
BA1			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

