

Variant: NM_000546.5(TP53):c.28G>A (p.Val10Ile)

Version: 2.0

CA000093 [↗](#)

127806 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 48c832f0-7992-455f-bf7e-15572c0d545d

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HGVS expressions

NM_000546.5:c.28G>A

NM_000546.5(TP53):c.28G>A (p.Val10Ile)

NC_000017.11:g.7676567C>T

CM000679.2:g.7676567C>T

NC_000017.10:g.7579885C>T

CM000679.1:g.7579885C>T

NC_000017.9:g.7520610C>T

NG_017013.2:g.15984G>A

ENST00000503591.2:c.28G>A

ENST00000508793.6:c.28G>A

ENST00000509690.6:c.-21-1331G>A

ENST00000514944.6:c.28G>A

ENST00000604348.6:c.28G>A

ENST00000269305.9:c.28G>A

ENST00000269305.8:c.28G>A

ENST00000359597.8:c.28G>A

ENST00000413465.6:c.28G>A

ENST00000420246.6:c.28G>A

ENST00000445888.6:c.28G>A

ENST00000455263.6:c.28G>A

ENST00000503591.1:c.28G>A

ENST00000505014.5:n.167G>A

ENST00000508793.5:c.28G>A

ENST00000509690.5:c.-21-1331G>A

ENST00000514944.5:c.28G>A

ENST00000604348.5:c.28G>A

ENST00000610292.4:c.-207G>A

ENST00000610538.4:c.-90G>A

ENST00000615910.4:c.28G>A

ENST00000617185.4:c.28G>A

ENST00000619485.4:c.-90G>A

ENST00000620739.4:c.-90G>A

ENST00000622645.4:c.-90G>A

ENST00000635293.1:c.-90G>A

NM_001126112.2:c.28G>A

NM_001126113.2:c.28G>A

NM_001126114.2:c.28G>A

NM_001126118.1:c.-207G>A
NM_001276695.1:c.-90G>A
NM_001276696.1:c.-90G>A
NM_001276760.1:c.-90G>A
NM_001276761.1:c.-90G>A
NM_001276695.2:c.-90G>A
NM_001276696.2:c.-90G>A
NM_001276760.2:c.-90G>A
NM_001276761.2:c.-90G>A
NM_000546.6:c.28G>A
NM_001126112.3:c.28G>A
NM_001126113.3:c.28G>A
NM_001126114.3:c.28G>A
NM_001126118.2:c.-207G>A
NM_001276695.3:c.-90G>A
NM_001276696.3:c.-90G>A
NM_001276760.3:c.-90G>A
NM_001276761.3:c.-90G>A

Benign

Met criteria codes 4

BP4 PM2_Supporting BS2 BS3

Not Met criteria codes 11

PS1 PS2 PS4 PP1 PP3 PP4
BA1 PM1 PM5 BS1 BS4

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.28G>A variant in TP53 is a missense variant predicted to cause substitution of Valine by Isoleucine at amino acid 10 (p.Val10Ile). This variant has been observed in at least 8 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; Internal lab contributors: SCV000184102.7). This variant has an allele frequency of .000021066 (34/1613962 alleles) across gnomAD v4.1.0 (after removing low AB alleles likely to represent CHIP contamination and recalculating total allele frequency) which is lower than the Clingen TP53 VCEP threshold (<0.00003) 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 = -0.0961; 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, PM2_Supporting, BS3, BP4_moderate. (Bayesian Points: -9; VCEP specifications version 2.0; 7/24/2024).

Met criteria codes

BP4			BP4_MODERATE Computational predictor scores (BayesDel = -0.0961; 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)
PM2_Supporting			This variant has an allele frequency of .000021066 (34/1613962 alleles) across gnomAD v4.1.0 (after removing low AB alleles likely to represent CHIP contamination and recalculating total allele frequency) which is lower than the ClinGen TP53 VCEP threshold (<0.00003) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
BS2			This variant has been observed in at least 8 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; Internal lab contributors: SCV000184102.7).
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 (BS3; PMIDs: 12826609, 29979965, 30224644).

Not Met criteria codes

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
PS4			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
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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			3 different missense variants with equal or lesser impact (c.29T>G, p.Val10Gly; c.28G>T, p.Val1-Phe; c.28G>C, p.Val10Leu) in the same codon have been reported (ClinVar Variation IDs: 822501, 968647, 231387). However, these

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).

BS1			Bring to Experts: V3.1.2 has AF of 0.0004960 in Other subpop - does this count?
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History



 

 

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