

Variant: NM_000546.5(TP53):c.145G>A (p.Asp49Asn)

CA000056 [↗](#)

186363 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 919a92fa-b50b-4d78-ad70-26b081a7dc4d

Approved on: 2024-08-05

Published on: 2024-08-05

HGVS expressions

NM_000546.5(TP53):c.145G>A (p.Asp49Asn)

NM_000546.5:c.145G>A

NC_000017.11:g.7676224C>T

CM000679.2:g.7676224C>T

NC_000017.10:g.7579542C>T

CM000679.1:g.7579542C>T

NC_000017.9:g.7520267C>T

NG_017013.2:g.16327G>A

ENST00000503591.2:c.145G>A

ENST00000508793.6:c.145G>A

ENST00000509690.6:c.-21-988G>A

ENST00000514944.6:c.96+158G>A

ENST00000604348.6:c.145G>A

ENST00000269305.9:c.145G>A

ENST00000269305.8:c.145G>A

ENST00000359597.8:c.145G>A

ENST00000413465.6:c.145G>A

ENST00000420246.6:c.145G>A

ENST00000445888.6:c.145G>A

ENST00000455263.6:c.145G>A

ENST00000503591.1:c.145G>A

ENST00000505014.5:n.401G>A

ENST00000508793.5:c.145G>A

ENST00000509690.5:c.-21-988G>A

ENST00000514944.5:c.96+158G>A

ENST00000604348.5:c.145G>A

ENST00000610292.4:c.28G>A

ENST00000610538.4:c.28G>A

ENST00000615910.4:c.145G>A

ENST00000617185.4:c.145G>A

ENST00000619485.4:c.28G>A

ENST00000620739.4:c.28G>A

ENST00000622645.4:c.28G>A

ENST00000635293.1:c.28G>A

NM_001126112.2:c.145G>A

NM_001126113.2:c.145G>A

NM_001126114.2:c.145G>A

NM_001126118.1:c.28G>A
NM_001276695.1:c.28G>A
NM_001276696.1:c.28G>A
NM_001276760.1:c.28G>A
NM_001276761.1:c.28G>A
NM_001276695.2:c.28G>A
NM_001276696.2:c.28G>A
NM_001276760.2:c.28G>A
NM_001276761.2:c.28G>A
NM_000546.6:c.145G>A
NM_001126112.3:c.145G>A
NM_001126113.3:c.145G>A
NM_001126114.3:c.145G>A
NM_001126118.2:c.28G>A
NM_001276695.3:c.28G>A
NM_001276696.3:c.28G>A
NM_001276760.3:c.28G>A
NM_001276761.3:c.28G>A

Benign

Met criteria codes 4

BS2 BS3 BP4 PM2_Supporting

Not Met criteria codes 10

PS2 PS1 PS3 PP4 PP1 PM1
PM5 BA1 BS4 BS1

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.145G>A variant in TP53 is a missense variant predicted to cause substitution of aspartic acid by asparagine at amino acid 49 (p.Asp49Asn). 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; ClinVar SCV: SCV000216702.6). This variant has an allele frequency of 0.0000111525 (18/1613988 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 = -0.232; Align GVG D Class C0) are below the recommended thresholds (BayesDel ≤ -0.008 and an Align GVG D 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

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; ClinVar SCV: SCV000216702.6).
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 = -0.232; 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 0.0000111525 (18/1613988 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).

Not Met criteria codes

PS2			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
PP4			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
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			4 different missense variants (c.147T>G, p.Asp49Glu; c.147T>A; p.Asp49Glu; c.146A>G, p.Asp49Gly; c.145G>C, p.Asp49His) in the same codon have been reported (ClinVar Variation IDs: 1506044, 1361888, 231133, 135948). 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).
BA1			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
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 



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See Report

◀ Preferred Variant Title

◀ Classification 

◀ Condition

◀ Published Date

◀ Version 

Criteria Specification

◀ Gene

No matching records found

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