

Variant: NM_001126112.2(TP53):c.145G>C (p.Asp49His)

Version: 2.0

CA000057 [↗](#)

135948 (ClinVar) [↗](#)

Gene: TP53 ([HGNC:7157](#))
Condition: Li-Fraumeni syndrome ([MONDO:0018875](#))
Inheritance Mode: Autosomal dominant inheritance
UUID: 3ae5f394-d710-4984-8d13-7c585ade67dc
Approved on: 2025/1/16
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HGVS expressions

NM_001126112.2(TP53):c.145G>C (p.Asp49His)
NM_001126112.2:c.145G>C
NC_000017.11:g.7676224C>G
CM000679.2:g.7676224C>G
NC_000017.10:g.7579542C>G
CM000679.1:g.7579542C>G
NC_000017.9:g.7520267C>G
NG_017013.2:g.16327G>C
ENST00000503591.2:c.145G>C
ENST00000508793.6:c.145G>C
ENST00000509690.6:c.-21-988G>C
ENST00000514944.6:c.96+158G>C
ENST00000604348.6:c.145G>C
ENST00000269305.9:c.145G>C
ENST00000269305.8:c.145G>C
ENST00000359597.8:c.145G>C
ENST00000413465.6:c.145G>C
ENST00000420246.6:c.145G>C
ENST00000445888.6:c.145G>C
ENST00000455263.6:c.145G>C
ENST00000503591.1:c.145G>C
ENST00000505014.5:n.401G>C
ENST00000508793.5:c.145G>C
ENST00000509690.5:c.-21-988G>C
ENST00000514944.5:c.96+158G>C
ENST00000604348.5:c.145G>C
ENST00000610292.4:c.28G>C
ENST00000610538.4:c.28G>C
ENST00000615910.4:c.145G>C
ENST00000617185.4:c.145G>C
ENST00000619485.4:c.28G>C
ENST00000620739.4:c.28G>C
ENST00000622645.4:c.28G>C
ENST00000635293.1:c.28G>C
NM_000546.5:c.145G>C
NM_001126113.2:c.145G>C
NM_001126114.2:c.145G>C

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

Benign

Met criteria codes 3

BP4 BS1 BS2_Supporting

Not Met criteria codes 17

BA1 BP1 BP2 BS4 BS3 PP1
PP2 PP3 PP4 PM2 PS1
PS2 PS3 PS4 PM1 PM3
PM5

Evidence Links 1

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.145G>C variant in TP53 is a missense variant predicted to cause substitution of aspartic acid by histidine at amino acid 49 (p.Asp49His). 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). The filtering allele frequency is 0.0007696 in the East Asian population in gnomAD v4.1.0, which is higher than the ClinGen TP53 VCEP threshold (≥ 0.0003 but < 0.001) for BS1, and therefore meets this criterion (BS1). In vitro assays performed in yeast and/or human cell lines showed conflicting results with respect to transactivation, growth suppression activity, and/or tetramer formation (PS3/BS3 not met; PMIDs: 12826609, 30224644, 15489903, 12901974, 18199664). Computational predictor scores (BayesDel = -0.0307; Align GVGD Class 0) 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). This variant has been reported as a putative founder variant in the Japanese population (PMID: 27545002). 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, BS1, BP4_Moderate. (Bayesian Points: -7; VCEP specifications version 2.1.0; 1/16/2025)

Met criteria codes

BP4			BP4_MODERATE Computational predictor scores (BayesDel = -0.0307; Align GVGD Class 0) 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).
BS1			The filtering allele frequency is 0.0007696 in the East Asian population in gnomAD v4.1.0, which is higher than the ClinGen TP53 VCEP threshold ($\geq$ 0.0003 but $<$ 0.001) for BS1, and therefore meets this criterion (BS1).
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). 3 female individuals cancer free by age 60 at Ambry.
Not Met criteria codes			
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			These evidence codes are not currently applicable for TP53 VCEP curations
BP2			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
BS3			In vitro assays performed in yeast and/or human cell lines showed conflicting results with respect to transactivation, growth suppression activity, and/or tetramer formation (PS3/BS3 not met; PMIDs: 12826609, 30224644, 15489903, 12901974, 18199664).
			Variant disrupts the human replication protein A (RPA)-binding domain without compromising transactivation function PubMed:15489903 
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			These evidence codes are not currently applicable for TP53 VCEP curations
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
PM2			

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			In vitro assays performed in yeast and/or human cell lines showed conflicting results with respect to transactivation, growth suppression activity, and/or tetramer formation (PS3/BS3 not met; PMIDs: 12826609, 30224644, 15489903, 12901974, 18199664). Variant disrupts the human replication protein A (RPA)-binding domain without compromising transactivation function PubMed:15489903 
PS4			This variant received a total of 0 points across dozens of unrelated probands (PS4 not met; PMIDs: 1565143, 27545002, 28902083, 29667044, 30287823, 33309985, 34863587, Internal lab contributors). Many cases were missing family history to fully assess potential point values.
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).
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			Four different missense variants (c.147T>G (p.Asp49Glu); c.147T>A (p.Asp49Glu); c.146A>G (p.Asp49Gly); c.145G>A (p.Asp49Asn)) in the same codon have been reported (ClinVar Variation ID: 1506044, 1361888, 231133, 186363). However, one is curated as benign by the ClinGen TP53 VCEP, and the other 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).

Curation History



 

 

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