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

Version: 2.0

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

PM1 PM5 BA1 BS4 BS1
PS2 PS1 PS3 PP4 PP1

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 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

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 ≤ -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).
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

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
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

Curation History

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