Variant: NM_000546.6(TP53):c.997C>T (p.Arg333Cys)

Version: 2.0

CA000530

184745 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4bdb59d3-0848-40a4-91d8-1adc8f8effef
Approved on: 2025-02-06
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HGVS expressions

NM_000546.6:c.997C>T
NM_000546.6(TP53):c.997C>T (p.Arg333Cys)
NC_000017.11:g.7670712G>A
CM000679.2:g.7670712G>A
NC_000017.10:g.7574030G>A
CM000679.1:g.7574030G>A
NC_000017.9:g.7514755G>A
NG_017013.2:g.21839C>T
ENST00000503591.2:c.997C>T
ENST00000508793.6:c.997C>T
ENST00000509690.6:c.601C>T
ENST00000514944.6:c.718C>T
ENST00000604348.6:c.976C>T
ENST00000269305.9:c.997C>T
ENST00000269305.8:c.997C>T
ENST00000359597.8:c.993+2823C>T
ENST00000413465.6:c.782+3469C>T
ENST00000420246.6:c.*104C>T
ENST00000445888.6:c.997C>T
ENST00000455263.6:c.*16C>T
ENST00000504290.5:c.*16C>T
ENST00000504937.5:c.601C>T
ENST00000510385.5:c.*104C>T
ENST00000576024.1:c.54-1022C>T
ENST00000610292.4:c.880C>T
ENST00000610538.4:c.*16C>T
ENST00000610623.4:c.*16C>T
ENST00000615910.4:c.964C>T
ENST00000617185.4:c.*104C>T
ENST00000618944.4:c.*104C>T
ENST00000619186.4:c.520C>T
ENST00000619485.4:c.880C>T
ENST00000620739.4:c.880C>T
ENST00000622645.4:c.*104C>T
ENST00000635293.1:c.880C>T
NM_000546.5:c.997C>T
NM_001126112.2:c.997C>T

NM_001126113.2:c.*16C>T
NM_001126114.2:c.*104C>T
NM_001126115.1:c.601C>T
NM_001126116.1:c.*104C>T
NM_001126117.1:c.*16C>T
NM_001126118.1:c.880C>T
NM_001276695.1:c.*16C>T
NM_001276696.1:c.*104C>T
NM_001276697.1:c.520C>T
NM_001276698.1:c.*104C>T
NM_001276699.1:c.*16C>T
NM_001276760.1:c.880C>T
NM_001276761.1:c.880C>T
NM_001276695.2:c.*16C>T
NM_001276696.2:c.*104C>T
NM_001276697.2:c.520C>T
NM_001276698.2:c.*104C>T
NM_001276699.2:c.*16C>T
NM_001276760.2:c.880C>T
NM_001276761.2:c.880C>T
NM_001126112.3:c.997C>T
NM_001126113.3:c.*16C>T
NM_001126114.3:c.*104C>T
NM_001126115.2:c.601C>T
NM_001126116.2:c.*104C>T
NM_001126117.2:c.*16C>T
NM_001126118.2:c.880C>T
NM_001276695.3:c.*16C>T
NM_001276696.3:c.*104C>T
NM_001276697.3:c.520C>T
NM_001276698.3:c.*104C>T
NM_001276699.3:c.*16C>T
NM_001276760.3:c.880C>T
NM_001276761.3:c.880C>T

Likely Benign

Met criteria codes 4

PM2_Supporting **PP3**
BS2_Supporting **BS3**

Not Met criteria codes 12

PS1 **PS2** **PS3** **PS4** **PP1** **PP4**
BA1 **PM1** **PM5** **BS1** **BS4**
BP4

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 2.2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: 997C>T variant in TP53 is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 333 (p.Arg333Cys). This variant was observed in an individual with breast cancer in their 20s who also had a VUS in the ATM gene. This variant has also been observed in 44 individuals that did not appear to have LFS across two commercial laboratories (PS4 not met; Internal lab contributors). 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). This variant has an allele frequency of 0.00001797 (29/1613610alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has a subpopulation allele frequency of <0.00004 in all non-bottleneck populations with 2 or more alleles present (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, 30224644). Computational predictor scores (BayesDel = 0.237; Align GVGD = Class 35) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3). In summary, this variant meets the criteria to be classified as Likely Benign for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2_Supporting, PM2_Supporting, BS3, PP3. (Bayesian Points: -3; VCEP specifications version 2.2; 2/6/2025)

Met criteria codes

PM2_Supporting	✓	This variant has an allele frequency of 0.00001797 (29/1613610alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has a subpopulation allele frequency of <0.00004 in all non-bottleneck populations with 2 or more alleles present (PM2_Supporting).
PP3	✓	Computational predictor scores (BayesDel = 0.237; Align GVGD = Class 35) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3).
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).
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, 30224644). showed comparable or higher expression levels of CDKN1A, MDM2, GADD45A and PMAIP1 compared to WT condition PubMed:39060302

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
PS3	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✗	

This variant was observed in an individual with breast cancer in their 20s who also had a VUS in the ATM gene. This variant has also been observed in 44 individuals that did not appear to have LFS across two commercial laboratories (PS4 not met; Internal lab contributors).

PP1	ⓘ	✗	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	ⓘ	✗	Another missense variant(c.998G>A, p.Arg333His) in the same codon has been reported (ClinVar Variation ID: 142273). However, this variant is classified as likely benign by the ClinGen TP53 VCEP's specifications (PM5 not met).
BS1	ⓘ	✗	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
BP4	ⓘ	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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