The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000546.5(TP53):c.1003C>T (p.Arg335Cys)

Version: 2.0

CA000009

141159 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 2c051651-783e-433a-913d-2201e71b6cb7
Approved on: 2025-02-06
Published on: 2025-02-07

HGVS expressions

NM_000546.5:c.1003C>T
NM_000546.5(TP53):c.1003C>T (p.Arg335Cys)
NC_000017.11:g.7670706G>A
CM000679.2:g.7670706G>A
NC_000017.10:g.7574024G>A
CM000679.1:g.7574024G>A
NC_000017.9:g.7514749G>A
NG_017013.2:g.21845C>T
ENST00000503591.2:c.1003C>T
ENST00000508793.6:c.1003C>T
ENST00000509690.6:c.607C>T
ENST00000514944.6:c.724C>T
ENST00000604348.6:c.982C>T
ENST00000269305.9:c.1003C>T
ENST00000269305.8:c.1003C>T
ENST00000359597.8:c.993+2829C>T
ENST00000413465.6:c.782+3475C>T
ENST00000420246.6:c.*110C>T
ENST00000445888.6:c.1003C>T
ENST00000455263.6:c.*22C>T
ENST00000504290.5:c.*22C>T
ENST00000504937.5:c.607C>T
ENST00000510385.5:c.*110C>T
ENST00000576024.1:c.54-1016C>T
ENST00000610292.4:c.886C>T
ENST00000610538.4:c.*22C>T
ENST00000610623.4:c.*22C>T
ENST00000615910.4:c.970C>T
ENST00000617185.4:c.*110C>T
ENST00000618944.4:c.*110C>T
ENST00000619186.4:c.526C>T
ENST00000619485.4:c.886C>T
ENST00000620739.4:c.886C>T
ENST00000622645.4:c.*110C>T
ENST00000635293.1:c.886C>T
NM_001126112.2:c.1003C>T
NM_001126113.2:c.*22C>T

NM_001126114.2:c.*110C>T
NM_001126115.1:c.607C>T
NM_001126116.1:c.*110C>T
NM_001126117.1:c.*22C>T
NM_001126118.1:c.886C>T
NM_001276695.1:c.*22C>T
NM_001276696.1:c.*110C>T
NM_001276697.1:c.526C>T
NM_001276698.1:c.*110C>T
NM_001276699.1:c.*22C>T
NM_001276760.1:c.886C>T
NM_001276761.1:c.886C>T
NM_001276695.2:c.*22C>T
NM_001276696.2:c.*110C>T
NM_001276697.2:c.526C>T
NM_001276698.2:c.*110C>T
NM_001276699.2:c.*22C>T
NM_001276760.2:c.886C>T
NM_001276761.2:c.886C>T
NM_000546.6:c.1003C>T
NM_001126112.3:c.1003C>T
NM_001126113.3:c.*22C>T
NM_001126114.3:c.*110C>T
NM_001126115.2:c.607C>T
NM_001126116.2:c.*110C>T
NM_001126117.2:c.*22C>T
NM_001126118.2:c.886C>T
NM_001276695.3:c.*22C>T
NM_001276696.3:c.*110C>T
NM_001276697.3:c.526C>T
NM_001276698.3:c.*110C>T
NM_001276699.3:c.*22C>T
NM_001276760.3:c.886C>T
NM_001276761.3:c.886C>T

Likely Benign

Met criteria codes 4

BS2_Supporting BS3 PM2_Supporting PP3

Not Met criteria codes 12

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

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 2.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.1003C>T variant in TP53 is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 335 (p.Arg335Cys). Although this variant has been observed in germline cases, to our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (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; ClinVar SCV: SCV000629764.4). This variant has an allele frequency of 0.000001859 (3/1613806 alleles) 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, 29979965, 30224644). Computational predictor scores (BayesDel = 0.275; Align GVGD = Class C25) 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

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; ClinVar SCV: SCV000629764.4).
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).
PM2_Supporting	✔	This variant has an allele frequency of 0.000001859 (3/1613806 alleles) 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 = 0.275; Align GVGD = Class C25) 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).

Not Met criteria codes

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
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS1	✖	No other variants with same amino acid change in ClinVar
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	✖	Although this variant has been observed in germline cases, to our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (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
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 (p.Arg335Leu, p.Arg335Pro, p.Arg335His) in the same codon have been reported. 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).

Curation History

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