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_000546.6(TP53):c.1009C>T (p.Arg337Cys)

Version: 1.0

CA000010

142536 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4424bcab-bb1a-4d11-bac2-48862c2e987b
Approved on: 2025-05-07
Published on: 2025-07-18

HGVS expressions

NM_000546.6:c.1009C>T
NM_000546.6(TP53):c.1009C>T (p.Arg337Cys)
NC_000017.11:g.7670700G>A
CM000679.2:g.7670700G>A
NC_000017.10:g.7574018G>A
CM000679.1:g.7574018G>A
NC_000017.9:g.7514743G>A
NG_017013.2:g.21851C>T
ENST00000503591.2:c.1009C>T
ENST00000508793.6:c.1009C>T
ENST00000509690.6:c.613C>T
ENST00000514944.6:c.730C>T
ENST00000604348.6:c.988C>T
ENST00000269305.9:c.1009C>T
ENST00000269305.8:c.1009C>T
ENST00000359597.8:c.993+2835C>T
ENST00000413465.6:c.782+3481C>T
ENST00000420246.6:c.*116C>T
ENST00000445888.6:c.1009C>T
ENST00000455263.6:c.*28C>T
ENST00000504290.5:c.*28C>T
ENST00000504937.5:c.613C>T
ENST00000510385.5:c.*116C>T
ENST00000576024.1:c.54-1010C>T
ENST00000610292.4:c.892C>T
ENST00000610538.4:c.*28C>T
ENST00000610623.4:c.*28C>T
ENST00000615910.4:c.976C>T
ENST00000617185.4:c.*116C>T
ENST00000618944.4:c.*116C>T
ENST00000619186.4:c.532C>T
ENST00000619485.4:c.892C>T
ENST00000620739.4:c.892C>T
ENST00000622645.4:c.*116C>T
ENST00000635293.1:c.892C>T
NM_000546.5:c.1009C>T
NM_001126112.2:c.1009C>T

NM_001126113.2:c.*28C>T
NM_001126114.2:c.*116C>T
NM_001126115.1:c.613C>T
NM_001126116.1:c.*116C>T
NM_001126117.1:c.*28C>T
NM_001126118.1:c.892C>T
NM_001276695.1:c.*28C>T
NM_001276696.1:c.*116C>T
NM_001276697.1:c.532C>T
NM_001276698.1:c.*116C>T
NM_001276699.1:c.*28C>T
NM_001276760.1:c.892C>T
NM_001276761.1:c.892C>T
NM_001276695.2:c.*28C>T
NM_001276696.2:c.*116C>T
NM_001276697.2:c.532C>T
NM_001276698.2:c.*116C>T
NM_001276699.2:c.*28C>T
NM_001276760.2:c.892C>T
NM_001276761.2:c.892C>T
NM_001126112.3:c.1009C>T
NM_001126113.3:c.*28C>T
NM_001126114.3:c.*116C>T
NM_001126115.2:c.613C>T
NM_001126116.2:c.*116C>T
NM_001126117.2:c.*28C>T
NM_001126118.2:c.892C>T
NM_001276695.3:c.*28C>T
NM_001276696.3:c.*116C>T
NM_001276697.3:c.532C>T
NM_001276698.3:c.*116C>T
NM_001276699.3:c.*28C>T
NM_001276760.3:c.892C>T
NM_001276761.3:c.892C>T

Pathogenic

Met criteria codes 8

PP3 PP4_Moderate PM5_Supporting PM2_Supporting PS2 PS3 PS4 PM1

Not Met criteria codes 4

PP1 BS1 BS3 BP4

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 2.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6(TP53):c.1009C>T variant in TP53 is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 337 (p.Arg337Cys). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with a strongly LFS-associated cancer and as a de novo occurrence with unconfirmed parental relationships in 1 individual with a moderately LFS-associated cancer totaling 5 phenotype points (PS2; PMID: 18511570, Internal lab contributors). This variant has been reported in 10 unrelated families meeting Revised Chompret; 1 family meeting classic; and reported in 1 individual under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 6.5 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMIDs: 1353190, 9452042; Internal lab contributors). At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, Internal lab contributors). This variant is absent from gnomAD v4.1.0 (PM2_Supporting).In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965). This variant has 36 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspot by the Clingen TP53 VCEP (≥ 10 somatic occurrences, PMID: 30311369) (PM1). Computational predictor scores (BayesDel = 0.316468; Align GVGD = Class C45) 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). Three missense variants (p.Arg337Ser, p.Arg337Pro, p.Arg337Leu) in the same codon have been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications.(PM5_Supporting). In summary, this variant meets the criteria to be classified as Pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS3, PM1, PS4, PP3, PP4_Moderate, PM2_Supporting, PM5_Supporting, PS2. (Bayesian Points: 19; VCEP specifications version 2.3)

Met criteria codes

PP3	✔	Computational predictor scores (BayesDel = 0.316468; Align GVGD = Class C45) 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).
PP4_Moderate	✔	At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, Internal lab contributors).
PM5_Supporting	✔	Three missense variants (p.Arg337Ser, p.Arg337Pro, p.Arg337Leu) in the same codon have been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications.(PM5_Supporting).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS2	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with a strongly LFS-associated cancer and as a de novo occurrence with unconfirmed parental relationships in 1 individual with a moderately LFS-associated cancer totaling 5 phenotype points (PS2; PMID: 18511570, Internal lab contributors).
PS3	✔	In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965).
PS4	✔	This variant has been reported in 10 unrelated families meeting Revised Chompret; 1 family meeting classic; and reported in 1 individual under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 6.5 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMIDs: 1353190, 9452042; Internal lab contributors).
PM1	✔	

This variant has 36 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspot by the Clingen TP53 VCEP (≥ 10 somatic occurrences, PMID: 30311369) (PM1).

Not Met criteria codes

PP1	✖	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
BS3	✖	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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