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.332T>G (p.Leu111Arg)

Version: 2.0

CA16603050

376631 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 96ab2334-8f49-48fc-a973-aa806a4567a1
Approved on: 2026/1/6
Published on: 2026/1/14

HGVS expressions

NM_000546.6:c.332T>G
NM_000546.6(TP53):c.332T>G (p.Leu111Arg)
NC_000017.11:g.7676037A>C
CM000679.2:g.7676037A>C
NC_000017.10:g.7579355A>C
CM000679.1:g.7579355A>C
NC_000017.9:g.7520080A>C
NG_017013.2:g.16514T>G
ENST00000503591.2:c.332T>G
ENST00000508793.6:c.332T>G
ENST00000509690.6:c.-21-801T>G
ENST00000514944.6:c.96+345T>G
ENST00000604348.6:c.332T>G
ENST00000269305.9:c.332T>G
ENST00000269305.8:c.332T>G
ENST00000359597.8:c.332T>G
ENST00000413465.6:c.332T>G
ENST00000420246.6:c.332T>G
ENST00000445888.6:c.332T>G
ENST00000455263.6:c.332T>G
ENST00000503591.1:c.332T>G
ENST00000505014.5:n.588T>G
ENST00000508793.5:c.332T>G
ENST00000509690.5:c.-21-801T>G
ENST00000514944.5:c.96+345T>G
ENST00000604348.5:c.332T>G
ENST00000610292.4:c.215T>G
ENST00000610538.4:c.215T>G
ENST00000615910.4:c.332T>G
ENST00000617185.4:c.332T>G
ENST00000619485.4:c.215T>G
ENST00000620739.4:c.215T>G
ENST00000622645.4:c.215T>G
ENST00000635293.1:c.215T>G
NM_000546.5:c.332T>G
NM_001126112.2:c.332T>G
NM_001126113.2:c.332T>G

NM_001126114.2:c.332T>G
NM_001126118.1:c.215T>G
NM_001276695.1:c.215T>G
NM_001276696.1:c.215T>G
NM_001276760.1:c.215T>G
NM_001276761.1:c.215T>G
NM_001276695.2:c.215T>G
NM_001276696.2:c.215T>G
NM_001276760.2:c.215T>G
NM_001276761.2:c.215T>G
NM_001126112.3:c.332T>G
NM_001126113.3:c.332T>G
NM_001126114.3:c.332T>G
NM_001126118.2:c.215T>G
NM_001276695.3:c.215T>G
NM_001276696.3:c.215T>G
NM_001276760.3:c.215T>G
NM_001276761.3:c.215T>G

Pathogenic

Met criteria codes 5

PS3 PM1_Supporting PM2_Supporting PM5 PP3_Moderate

Not Met criteria codes 20

PS1 PS2 PS4 BP5 BP7 BP4 BP3 BP1 BP2 PP1 PP2 PP4 PM6 PM3 PM4 BA1 PVS1 BS1 BS4 BS3

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 2.4.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.332T>G variant in TP53 is a missense variant predicted to cause substitution of leucine by arginine at amino acid 111 (p.Leu111Arg). To our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met). 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). Computational predictor scores (BayesDel = 0.4821; Align GVGD = Class 65) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate). This variant has 6 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 (2-9 somatic occurrences, PMID: 30311369) (PM1_Supporting). Another missense variant (c.332T>C, p.Leu111Pro) (ClinVar Variation ID: 376630), in the same codon has been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications.(PM5). In summary, this variant meets the criteria to be classified as likely pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS3, PP3_moderate, PM1_supporting, PM5, PM2_supporting. (Bayesian Points: 10; VCEP specifications version 2.4)

Met criteria codes

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).
PM1_Supporting	✔	This variant has 6 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 (2-9 somatic occurrences, PMID: 30311369) (PM1_Supporting).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PM5	✔	Another missense variant (c.332T>C, p.Leu111Pro) (ClinVar Variation ID: 376630), in the same codon has been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications.(PM5).
PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.4821; Align GVGD = Class 65) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate).

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
PS4	✖	To our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met).
BP5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	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
BP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.6(TP53):c.332T>G (p.Leu1…	Pathogenic	Li-Fraumeni Syndrome	2026-01-14	2.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.4.0	TP53
View	NM_000546.6(TP53):c.332T>G (p.Leu1…	Likely Pathogenic	Li-Fraumeni Syndrome	2025-12-05	1.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.3.0	TP53

Showing 1 to 2 of 2 rows

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