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>C (p.Leu111Pro)

Version: 1.0

CA16603049

376630 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: e9d8b95e-3168-46c1-a3a2-8512ee14d51c
Approved on: 2025/12/5
Published on: 2025/12/5

HGVS expressions

NM_000546.6:c.332T>C
NM_000546.6(TP53):c.332T>C (p.Leu111Pro)
NC_000017.11:g.7676037A>G
CM000679.2:g.7676037A>G
NC_000017.10:g.7579355A>G
CM000679.1:g.7579355A>G
NC_000017.9:g.7520080A>G
NG_017013.2:g.16514T>C
ENST00000503591.2:c.332T>C
ENST00000508793.6:c.332T>C
ENST00000509690.6:c.-21-801T>C
ENST00000514944.6:c.96+345T>C
ENST00000604348.6:c.332T>C
ENST00000269305.9:c.332T>C
ENST00000269305.8:c.332T>C
ENST00000359597.8:c.332T>C
ENST00000413465.6:c.332T>C
ENST00000420246.6:c.332T>C
ENST00000445888.6:c.332T>C
ENST00000455263.6:c.332T>C
ENST00000503591.1:c.332T>C
ENST00000505014.5:n.588T>C
ENST00000508793.5:c.332T>C
ENST00000509690.5:c.-21-801T>C
ENST00000514944.5:c.96+345T>C
ENST00000604348.5:c.332T>C
ENST00000610292.4:c.215T>C
ENST00000610538.4:c.215T>C
ENST00000615910.4:c.332T>C
ENST00000617185.4:c.332T>C
ENST00000619485.4:c.215T>C
ENST00000620739.4:c.215T>C
ENST00000622645.4:c.215T>C
ENST00000635293.1:c.215T>C
NM_000546.5:c.332T>C
NM_001126112.2:c.332T>C
NM_001126113.2:c.332T>C

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

Pathogenic

Met criteria codes 6

PP3_Moderate PS3 PS4_Moderate PP4_Moderate PM1_Supporting PM2_Supporting

Not Met criteria codes 10

PP2 PM4 BA1 PVS1 BS1 BS3 BP7 BP4 BP3 BP1

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: c.332T>C variant in TP53 is a missense variant predicted to cause substitution of leucine by proline at amino acid 111 (p.Leu111Pro). This variant has been reported in 3 probands meeting Revised Chompret criteria and 1 additional individual with HER2+ breast cancer under age 40. Based on this evidence, this variant scores 2 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; 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). Computational predictor scores (BayesDel = 0.4624; 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 7 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). 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: PS4_Moderate, PP4_Moderate, PS3, PP3_moderate, PM2_supporting, PM1_supporting. (Bayesian Points: 12; VCEP specifications version 2.3)

Met criteria codes

PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.4624; 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).
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_Moderate	✔	This variant has been reported in 3 probands meeting Revised Chompret criteria and 1 additional individual with HER2+ breast cancer under age 40. Based on this evidence, this variant scores 2 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; Internal lab contributors).
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).
PM1_Supporting	✔	This variant has 7 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).

Not Met criteria codes

PP2	✖	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	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	✖	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
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

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
⌑ Powered by BCM's Genboree.