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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(TP53):c.332T>C (p.Leu111Pro)
NM_000546.6:c.332T>C
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

PM1_Supporting PS4_Moderate PP3_Moderate PM2_Supporting PP4_Moderate PS3

Not Met criteria codes 10

BA1 PM4 BS1 BS3 BP7 BP4 BP3 BP1 PVS1 PP2

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

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).
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).
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).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
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).
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).

Not Met criteria codes

BA1	✖	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
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
PVS1	✖	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

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.6(TP53):c.332T>C (p.Leu1...	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 1 of 1 rows

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