

## Variant: *NM\_000546.5(TP53):c.1031T>C (p.Leu344Pro)*

Version: 1.1

CA000021 [↗](#)

12375 (ClinVar) [↗](#)

**Gene:** TP53 ([HGNC:7157](#))

**Condition:** Li-Fraumeni syndrome ([MONDO:0018875](#))

**Inheritance Mode:** Autosomal dominant inheritance

**UID:** 7b4332f9-03a6-43f1-afde-508d91bd92d5

**Approved on:** 2024-08-05

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### *HGVS expressions*

#### **NM\_000546.5:c.1031T>C**

NM\_000546.5(TP53):c.1031T>C (p.Leu344Pro)

NC\_000017.11:g.7670678A>G

CM000679.2:g.7670678A>G

NC\_000017.10:g.7573996A>G

CM000679.1:g.7573996A>G

NC\_000017.9:g.7514721A>G

NG\_017013.2:g.21873T>C

ENST00000503591.2:c.1031T>C

ENST00000508793.6:c.1031T>C

ENST00000509690.6:c.635T>C

ENST00000514944.6:c.752T>C

ENST00000604348.6:c.1010T>C

ENST00000269305.9:c.1031T>C

ENST00000269305.8:c.1031T>C

ENST00000359597.8:c.993+2857T>C

ENST00000413465.6:c.782+3503T>C

ENST00000420246.6:c.\*138T>C

ENST00000445888.6:c.1031T>C

ENST00000455263.6:c.\*50T>C

ENST00000504290.5:c.\*50T>C

ENST00000504937.5:c.635T>C

ENST00000510385.5:c.\*138T>C

ENST00000576024.1:c.54-988T>C

ENST00000610292.4:c.914T>C

ENST00000610538.4:c.\*50T>C

ENST00000610623.4:c.\*50T>C

ENST00000615910.4:c.998T>C

ENST00000617185.4:c.\*138T>C

ENST00000618944.4:c.\*138T>C

ENST00000619186.4:c.554T>C

ENST00000619485.4:c.914T>C

ENST00000620739.4:c.914T>C

ENST00000622645.4:c.\*138T>C

ENST00000635293.1:c.914T>C

NM\_001126112.2:c.1031T>C

NM\_001126113.2:c.\*50T>C

NM\_001126114.2:c.\*138T>C  
NM\_001126115.1:c.635T>C  
NM\_001126116.1:c.\*138T>C  
NM\_001126117.1:c.\*50T>C  
NM\_001126118.1:c.914T>C  
NM\_001276695.1:c.\*50T>C  
NM\_001276696.1:c.\*138T>C  
NM\_001276697.1:c.554T>C  
NM\_001276698.1:c.\*138T>C  
NM\_001276699.1:c.\*50T>C  
NM\_001276760.1:c.914T>C  
NM\_001276761.1:c.914T>C  
NM\_001276695.2:c.\*50T>C  
NM\_001276696.2:c.\*138T>C  
NM\_001276697.2:c.554T>C  
NM\_001276698.2:c.\*138T>C  
NM\_001276699.2:c.\*50T>C  
NM\_001276760.2:c.914T>C  
NM\_001276761.2:c.914T>C  
NM\_000546.6:c.1031T>C  
NM\_001126112.3:c.1031T>C  
NM\_001126113.3:c.\*50T>C  
NM\_001126114.3:c.\*138T>C  
NM\_001126115.2:c.635T>C  
NM\_001126116.2:c.\*138T>C  
NM\_001126117.2:c.\*50T>C  
NM\_001126118.2:c.914T>C  
NM\_001276695.3:c.\*50T>C  
NM\_001276696.3:c.\*138T>C  
NM\_001276697.3:c.554T>C  
NM\_001276698.3:c.\*138T>C  
NM\_001276699.3:c.\*50T>C  
NM\_001276760.3:c.914T>C  
NM\_001276761.3:c.914T>C

Likely Pathogenic

Met criteria codes 4

PS4\_Supporting PS3  
PM2\_Supporting PP3\_Moderate

Not Met criteria codes 16

PS1 PS2 BA1 PP1 PP4  
PVS1 PM1 PM5 PM4 BS2  
BS1 BS4 BS3 BP4 BP3 BP7

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 2.0.0](#)

[Criteria Specification Approval History](#)









[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel










TP53 VCEP





















The NM\_000546.6:c.1031T>C variant in TP53 is a missense variant predicted to cause substitution of leucine by proline at amino acid 344 (p.Leu344Pro). This variant has been reported in 1 proband meeting Classic criteria, and 1 proband meeting revised Chompret criteria. Based on this evidence, this variant scores 1.5 total points meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4\_Supporting PMID: 8649785, 20522432). This variant has an allele frequency of 6.195e-7 (1/1614076 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2\_Supporting, and therefore meets this criterion (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 (PMIDs: 12826609, 30224644, 29979965) (PS3). Computational predictor scores (BayesDel = 0.4856; 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). In summary, this variant meets criteria to be classified as likely pathogenic for Li-Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the TP53 Variant Curation Expert Panel: PM2\_Supporting, PP3\_Moderate, PS3, PS4\_Supporting (Bayesian Points: 8; VCEP specifications version 2.0; 7/24/2024).

#### Met criteria codes

<b>PS4_Supporting</b>			This variant has been reported in 1 proband meeting Classic criteria, and 1 proband meeting revised Chompret criteria. Based on this evidence, this variant scores 1.5 total points meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMID: 8649785, 20522432).
<b>PS3</b>			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).
<b>PM2_Supporting</b>			This variant has an allele frequency of 6.195e-7 (1/1614076 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
<b>PP3_Moderate</b>			Computational predictor scores (BayesDel = 0.4856; 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

<b>PS1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PS2</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BA1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PP1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PP4</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

<b>PVS1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PM1</b>			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).
<b>PM5</b>			2 different missense variants (c.1030C>A, p.Leu344Met and c.1030C>G, p.Leu344Val) in the same codon have been reported (ClinVar Variation ID: 1771001, 956897). 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).
<b>PM4</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BS2</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BS1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BS4</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BS3</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP4</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP3</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP7</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 

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