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_000546.5(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
UUID: 7b4332f9-03a6-43f1-afde-508d91bd92d5
Approved on: 2024/8/5
Published on: 2024/8/5

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 BP7 BP4 BP3 PP1 PP4 PM1 PM5 PM4 BA1 BS2 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 2.0.0*
- **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

PS4_Supporting	✔	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).
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).
PM2_Supporting	✔	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).
PP3_Moderate	✔	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

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
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

PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1		✖	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).
PM5		✖	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).
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
BS2		✖	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
BS4		✖	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

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.5(TP53):c.1031T>C (p.Leu...	Likely Pathogenic	Li-Fraumeni Syndrome	2024-08-05	1.1	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0	TP53
View	NM_000546.5(TP53):c.1031T>C (p.Leu...	Likely Pathogenic	Li-Fraumeni Syndrome	2020-01-24	1.0	-	TP53

Showing 1 to 2 of 2 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.