

Variant: NM_000546.6(TP53):c.1031T>G (p.Leu344Arg)

Version: 1.0

CA397832502 [↗](#)

2758378 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 18d0d2fa-742f-4ec6-b0d5-5ae1682e44c4

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HGVS expressions

NM_000546.6(TP53):c.1031T>G (p.Leu344Arg)

NM_000546.6:c.1031T>G

NC_000017.11:g.7670678A>C

CM000679.2:g.7670678A>C

NC_000017.10:g.7573996A>C

CM000679.1:g.7573996A>C

NC_000017.9:g.7514721A>C

NG_017013.2:g.21873T>G

ENST00000503591.2:c.1031T>G

ENST00000508793.6:c.1031T>G

ENST00000509690.6:c.635T>G

ENST00000514944.6:c.752T>G

ENST00000604348.6:c.1010T>G

ENST00000269305.9:c.1031T>G

ENST00000269305.8:c.1031T>G

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

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

ENST00000420246.6:c.*138T>G

ENST00000445888.6:c.1031T>G

ENST00000455263.6:c.*50T>G

ENST00000504290.5:c.*50T>G

ENST00000504937.5:c.635T>G

ENST00000510385.5:c.*138T>G

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

ENST00000610292.4:c.914T>G

ENST00000610538.4:c.*50T>G

ENST00000610623.4:c.*50T>G

ENST00000615910.4:c.998T>G

ENST00000617185.4:c.*138T>G

ENST00000618944.4:c.*138T>G

ENST00000619186.4:c.554T>G

ENST00000619485.4:c.914T>G

ENST00000620739.4:c.914T>G

ENST00000622645.4:c.*138T>G

ENST00000635293.1:c.914T>G

NM_000546.5:c.1031T>G

NM_001126112.2:c.1031T>G

NM_001126113.2:c.*50T>G
NM_001126114.2:c.*138T>G
NM_001126115.1:c.635T>G
NM_001126116.1:c.*138T>G
NM_001126117.1:c.*50T>G
NM_001126118.1:c.914T>G
NM_001276695.1:c.*50T>G
NM_001276696.1:c.*138T>G
NM_001276697.1:c.554T>G
NM_001276698.1:c.*138T>G
NM_001276699.1:c.*50T>G
NM_001276760.1:c.914T>G
NM_001276761.1:c.914T>G
NM_001276695.2:c.*50T>G
NM_001276696.2:c.*138T>G
NM_001276697.2:c.554T>G
NM_001276698.2:c.*138T>G
NM_001276699.2:c.*50T>G
NM_001276760.2:c.914T>G
NM_001276761.2:c.914T>G
NM_001126112.3:c.1031T>G
NM_001126113.3:c.*50T>G
NM_001126114.3:c.*138T>G
NM_001126115.2:c.635T>G
NM_001126116.2:c.*138T>G
NM_001126117.2:c.*50T>G
NM_001126118.2:c.914T>G
NM_001276695.3:c.*50T>G
NM_001276696.3:c.*138T>G
NM_001276697.3:c.554T>G
NM_001276698.3:c.*138T>G
NM_001276699.3:c.*50T>G
NM_001276760.3:c.914T>G
NM_001276761.3:c.914T>G

Likely Pathogenic

Met criteria codes 4

- PM2_Supporting
- PP3_Moderate
- PS3
- PM5_Supporting

Not Met criteria codes 7

- BS1
- BS3
- BP4
- PS1
- PS4
- BA1
- PM1

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.1031T>G variant in TP53 is a missense variant predicted to cause substitution of leucine by arginine at amino acid 344 (p.Leu344Arg). Although this variant has been observed in germline cases, to our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met; PMID: 34196900, 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 as well as impaired tetramer formation (PMIDs: 12826609, 30224644 16007150) (PS3). Computational predictor scores (BayesDel = 0.2882; 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). Another missense variant (c.1031T>C, p.Leu344Pro) (ClinVar Variation ID: 12375), in the same codon has been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP’s specifications.(PM5_Supporting). 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: PM2_Supporting, PS3, PP3_Moderate, PM5_Supporting. (Bayesian Points: 8; VCEP specifications version 2.4)

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP3_Moderate			Computational predictor scores (BayesDel = 0.2882; 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 by the majority of available assays indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965, 39774325).
PM5_Supporting			Another missense variant (c.1031T>C, p.Leu344Pro) (ClinVar Variation ID: 12375), in the same codon has been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP’s specifications. (PM5_Supporting).

Not Met criteria codes

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
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			Although this variant has been observed in germline cases, to our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met; PMID: 34196900, Internal lab contributors).

BA1			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).

Curation History 		
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