

Variant: NM_000546.5(TP53):c.11C>T (p.Pro4Leu)

Version: 2.0

CA10583686 [↗](#)

237941 (ClinVar) [↗](#)

Gene: TP53 ([HGNC:7157](#))
Condition: Li-Fraumeni syndrome ([MONDO:0018875](#))
Inheritance Mode: Autosomal dominant inheritance
UUID: 410f531a-d916-4dbc-9751-ea42adb439f2
Approved on: 2025/1/16
Published on: 2025/1/16

HGVS expressions

NM_000546.5:c.11C>T
NM_000546.5(TP53):c.11C>T (p.Pro4Leu)
NC_000017.11:g.7676584G>A
CM000679.2:g.7676584G>A
NC_000017.10:g.7579902G>A
CM000679.1:g.7579902G>A
NC_000017.9:g.7520627G>A
NG_017013.2:g.15967C>T
ENST00000503591.2:c.11C>T
ENST00000508793.6:c.11C>T
ENST00000509690.6:c.-21-1348C>T
ENST00000514944.6:c.11C>T
ENST00000604348.6:c.11C>T
ENST00000269305.9:c.11C>T
ENST00000269305.8:c.11C>T
ENST00000359597.8:c.11C>T
ENST00000413465.6:c.11C>T
ENST00000420246.6:c.11C>T
ENST00000445888.6:c.11C>T
ENST00000455263.6:c.11C>T
ENST00000503591.1:c.11C>T
ENST00000505014.5:n.150C>T
ENST00000508793.5:c.11C>T
ENST00000509690.5:c.-21-1348C>T
ENST00000514944.5:c.11C>T
ENST00000604348.5:c.11C>T
ENST00000610292.4:c.-224C>T
ENST00000610538.4:c.-107C>T
ENST00000615910.4:c.11C>T
ENST00000617185.4:c.11C>T
ENST00000619485.4:c.-107C>T
ENST00000620739.4:c.-107C>T
ENST00000622645.4:c.-107C>T
ENST00000635293.1:c.-107C>T
NM_001126112.2:c.11C>T
NM_001126113.2:c.11C>T
NM_001126114.2:c.11C>T

NM_001126118.1:c.-224C>T
NM_001276695.1:c.-107C>T
NM_001276696.1:c.-107C>T
NM_001276760.1:c.-107C>T
NM_001276761.1:c.-107C>T
NM_001276695.2:c.-107C>T
NM_001276696.2:c.-107C>T
NM_001276760.2:c.-107C>T
NM_001276761.2:c.-107C>T
NM_000546.6:c.11C>T
NM_001126112.3:c.11C>T
NM_001126113.3:c.11C>T
NM_001126114.3:c.11C>T
NM_001126118.2:c.-224C>T
NM_001276695.3:c.-107C>T
NM_001276696.3:c.-107C>T
NM_001276760.3:c.-107C>T
NM_001276761.3:c.-107C>T

Likely Benign

Met criteria codes 3

BS3 BP4 PM2_Supporting

Not Met criteria codes 15

PM1 PM5 BS2 BS1 BS4
PVS1 PS1 PS2 PS3 PS4
BP7 BA1 PP1 PP3 PP4

Evidence Links 3

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.11C>T variant in TP53 is a missense variant predicted to cause substitution of proline by leucine at amino acid 4 (p.Pro4Leu). This variant has an allele frequency of 6.196e-7 (1/1613946 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 functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 29979965, 30224644). Computational predictor scores (BayesDel = 0.062909; Align GVGD Class C0) are below the recommended thresholds (BayesDel < 0.16 and > -0.008 and an Align GVGD Class ≤ 55), evidence that does not predict a damaging effect on TP53 via protein change. SpliceAI predicts that the variant has no impact on splicing (BP4). In summary, this variant meets the criteria to be classified as Likely Benign for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PM2_Supporting, BS3, BP4. (Bayesian Points: -4; VCEP specifications version 2.0; 1/16/2025)

Met criteria codes

BS3



In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 29979965,

30224644).

Functional (94.3%% mean transactivation activity (>75%)) [PubMed:12826609](#)

No dominant negative effect (p53WTNutlin3 Z-score -0.367(< 0.61)), and no loss of function (Etoposide Z-score 0.356(> -0.21)). [PubMed:30224644](#)

N/A [PubMed:29979965](#)

BP4			Computational predictor scores (BayesDel = 0.062909; Align GVGD Class C0) are below the recommended thresholds (BayesDel < 0.16 and > -0.008 and an Align GVGD Class ≤ 55), evidence that does not predict a damaging effect on TP53 via protein change. SpliceAI predicts that the variant has no impact on splicing (BP4).
PM2_Supporting			This variant has an allele frequency of 6.196e-7 (1/1613946 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).

Not Met criteria codes

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			4 different missense variants (p.Pro4Gln, p.Pro4Arg, p.Pro4Ala, p.Pro4Ser) in the same codon have been reported (ClinVar Variation IDs: 2450740, 406582, 2848843, 1485939). However, the variants have not yet been curated to determine if they would be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP’s specifications (PM5 not evaluated).
BS2			Observed in 1 60+ year old cancer free female from internal laboratory data
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
PVS1			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
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			

			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
BA1			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
PP3			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

Curation History 		
		
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.