

Variant: NM_000546.6(TP53):c.-29+1G>T

Version: 1.0

CA2635892666 [↗](#)

2697350 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 47cd402e-b8b7-4a6a-b800-9621b436f16b

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HGVS expressions

NM_000546.6:c.-29+1G>T

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NC_000017.11:g.7687376C>A

CM000679.2:g.7687376C>A

NC_000017.10:g.7590694C>A

CM000679.1:g.7590694C>A

NC_000017.9:g.7531419C>A

NG_017013.2:g.5175G>T

NG_028245.1:g.6306C>A

ENST00000503591.2:c.-132+1G>T

ENST00000509690.6:c.-22+1G>T

ENST00000514944.6:c.-29+1G>T

ENST00000571370.2:n.148G>T

ENST00000604348.6:c.-29+1G>T

ENST00000269305.9:c.-29+1G>T

ENST00000269305.8:c.-29+1G>T

ENST00000316024.9:c.-1273C>A

ENST00000420246.6:c.-29+1G>T

ENST00000431639.6:c.-2+1152C>A

ENST00000445888.6:c.-26+1G>T

ENST00000455263.6:c.-29+1G>T

ENST00000503591.1:c.-132+1G>T

ENST00000505014.5:n.111+1G>T

ENST00000509690.5:c.-22+1G>T

ENST00000514944.5:c.-29+1G>T

ENST00000604348.5:c.-29+1G>T

ENST00000610292.4:c.-263+1G>T

ENST00000610538.4:c.-146+1G>T

ENST00000617185.4:c.-29+1G>T

ENST00000619485.4:c.-143+1G>T

ENST00000620739.4:c.-146+1G>T

ENST00000622645.4:c.-146+1G>T

ENST00000635293.1:c.-146+1G>T

NM_000546.5:c.-29+1G>T

NM_001126112.2:c.-26+1G>T

NM_001126113.2:c.-29+1G>T

NM_001126114.2:c.-29+1G>T

NM_001126118.1:c.-263+1G>T
NM_001143990.1:c.-2+1152C>A
NM_001276695.1:c.-146+1G>T
NM_001276696.1:c.-146+1G>T
NM_001276760.1:c.-146+1G>T
NM_001276761.1:c.-143+1G>T
NM_001276695.2:c.-146+1G>T
NM_001276696.2:c.-146+1G>T
NM_001276760.2:c.-146+1G>T
NM_001276761.2:c.-143+1G>T
NM_001126112.3:c.-26+1G>T
NM_001126113.3:c.-29+1G>T
NM_001126114.3:c.-29+1G>T
NM_001126118.2:c.-263+1G>T
NM_001143990.2:c.-2+1152C>A
NM_001276695.3:c.-146+1G>T
NM_001276696.3:c.-146+1G>T
NM_001276760.3:c.-146+1G>T
NM_001276761.3:c.-143+1G>T

Likely Pathogenic

Met criteria codes **6**

PP1 PP3 PP4 PVS1_Moderate
PS4_Moderate PM2_Supporting

Not Met criteria codes **9**

BS1 BS4 BS3 BS2 BP4 PS2
PS3 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 2.3.0*

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP











The NM_000546.6 c.-29+1G>T variant is a TP53 variant within a canonical donor site in the 5' untranslated region. Splicing assay data provides experimental evidence that this variant results in RNA transcript(s) with loss of function (PVS1_Moderate (RNA); Internal data contributor). This variant has been reported in 2 families meeting Classic criteria. Based on this evidence, this variant scores 2 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMID: 10980596). The variant has been reported to segregate with LFS-associated cancers in 3-4 meioses in 2 families (PP1; Internal lab contributors). At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, Internal lab contributor). This variant is absent from gnomAD v4.1.0 (PM2_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: PVS1_Moderate (RNA), PS4_Moderate, PP1, PP4, PM2_Supporting. (Bayesian Points: 7; VCEP specifications version 2.3)

Met criteria codes

















PP1



The variant has been reported to segregate with LFS-associated cancers in 3-4 meioses in 2 families (PP1; Internal lab contributors).

PP3			The computational splicing predictor SpliceAI gives a score of 0.98, predicting that the variant has an impact on splicing (score threshold > 0.20) (PP3).
PP4			At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, Internal lab contributor).
PVS1_Moderate			The NM_000546.6 c.-29+1G>C variant is a TP53 variant within a canonical donor site in the 5' untranslated region. Splicing assay data provides experimental evidence that this variant results in RNA transcript(s) with loss of function (PVS1_Moderate (RNA); Internal data contributor).
PS4_Moderate			This variant has been reported in 2 families meeting Classic criteria. Based on this evidence, this variant scores 1 total point meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Supporting; PMID: 10980596).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

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
BS2			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
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
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM1



No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History [↗](#)

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