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_000546.6(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
Approved on: 2025/12/5
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HGVS expressions

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

PVS1_Moderate PP1 PP3 PP4 PS4_Moderate PM2_Supporting

Not Met criteria codes 9

BP4 BS2 BS1 BS4 BS3 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

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).

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).
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

BP4	✖	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
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
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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