Variant: NM_001126112.2(TP53):c.509C>T (p.Thr170Met)

Version: 2.0

CA000246

184014 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: f2fc6a36-08b0-4d07-83a2-f60e3aed090e
Approved on: 2025-02-07
Published on: 2025-02-07

HGVS expressions

NM_001126112.2:c.509C>T
NM_001126112.2(TP53):c.509C>T (p.Thr170Met)
NC_000017.11:g.7675103G>A
CM000679.2:g.7675103G>A
NC_000017.10:g.7578421G>A
CM000679.1:g.7578421G>A
NC_000017.9:g.7519146G>A
NG_017013.2:g.17448C>T
ENST00000503591.2:c.509C>T
ENST00000508793.6:c.509C>T
ENST00000509690.6:c.113C>T
ENST00000514944.6:c.230C>T
ENST00000604348.6:c.488C>T
ENST00000269305.9:c.509C>T
ENST00000269305.8:c.509C>T
ENST00000359597.8:c.509C>T
ENST00000413465.6:c.509C>T
ENST00000420246.6:c.509C>T
ENST00000445888.6:c.509C>T
ENST00000455263.6:c.509C>T
ENST00000504290.5:c.113C>T
ENST00000504937.5:c.113C>T
ENST00000505014.5:n.765C>T
ENST00000509690.5:c.113C>T
ENST00000510385.5:c.113C>T
ENST00000514944.5:c.230C>T
ENST00000574684.1:n.17C>T
ENST00000610292.4:c.392C>T
ENST00000610538.4:c.392C>T
ENST00000610623.4:c.32C>T
ENST00000615910.4:c.476C>T
ENST00000617185.4:c.509C>T
ENST00000618944.4:c.32C>T
ENST00000619186.4:c.32C>T
ENST00000619485.4:c.392C>T
ENST00000620739.4:c.392C>T
ENST00000622645.4:c.392C>T

ENST00000635293.1:c.392C>T
NM_000546.5:c.509C>T
NM_001126113.2:c.509C>T
NM_001126114.2:c.509C>T
NM_001126115.1:c.113C>T
NM_001126116.1:c.113C>T
NM_001126117.1:c.113C>T
NM_001126118.1:c.392C>T
NM_001276695.1:c.392C>T
NM_001276696.1:c.392C>T
NM_001276697.1:c.32C>T
NM_001276698.1:c.32C>T
NM_001276699.1:c.32C>T
NM_001276760.1:c.392C>T
NM_001276761.1:c.392C>T
NM_001276695.2:c.392C>T
NM_001276696.2:c.392C>T
NM_001276697.2:c.32C>T
NM_001276698.2:c.32C>T
NM_001276699.2:c.32C>T
NM_001276760.2:c.392C>T
NM_001276761.2:c.392C>T
NM_000546.6:c.509C>T
NM_001126112.3:c.509C>T
NM_001126113.3:c.509C>T
NM_001126114.3:c.509C>T
NM_001126115.2:c.113C>T
NM_001126116.2:c.113C>T
NM_001126117.2:c.113C>T
NM_001126118.2:c.392C>T
NM_001276695.3:c.392C>T
NM_001276696.3:c.392C>T
NM_001276697.3:c.32C>T
NM_001276698.3:c.32C>T
NM_001276699.3:c.32C>T
NM_001276760.3:c.392C>T
NM_001276761.3:c.392C>T

Likely Benign

Met criteria codes 3

BS3_Supporting PM2_Supporting BS2

Not Met criteria codes 18

BA1 BP4 BP3 BP2 BP7 BS1 BS4 PP1 PP3 PS1 PS2 PS3 PS4 PM6 PM1 PM5 PM4 PVS1

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 2.2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.509C>T variant in TP53 is a missense variant predicted to cause substitution of threonine by methionine at amino acid 170 (p.Thr170Met). This variant has been observed in 4-7 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Moderate; Internal lab contributor). This variant has an allele frequency of 0.00003293 (3/91094 alleles) in the South Asian population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation, and retained growth suppression activity indicating that this variant does not impact protein function (BS3_Supporting; PMIDs: 12826609, 29979965, 30224644). 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: BS2_Moderate, BS3_Supporting, PM2_Supporting. (Bayesian Points: -2; VCEP specifications version 2.1; 2/6/2025)

Met criteria codes

BS3_Supporting	✓	In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation, and retained growth suppression activity indicating that this variant does not impact protein function (BS3_Supporting; PMIDs: 12826609, 29979965, 30224644).
PM2_Supporting	✓	This variant has an allele frequency of 0.00003293 (3/91094 alleles) in the South Asian population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
BS2	✓	BS2_MODERATE This variant has been observed in 4-7 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Moderate; Internal lab contributor).

Not Met criteria codes

BA1	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✗	The results from the computational predictors BayesDel and AlignGVGD do not agree, providing no evidence that correlates with a damaging or benign impact on TP53 function via protein change. Additionally, SpliceAI predicts that the variant has no impact on splicing (score threshold ≤ 0.10) (PP3 and BP4 not met).
BP3	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✗	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

BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	ℹ	✖	The results from the computational predictors BayesDel and AlignGVGD do not agree, providing no evidence that correlates with a damaging or benign impact on TP53 function via protein change. Additionally, SpliceAI predicts that the variant has no impact on splicing (score threshold ≤ 0.10) (PP3 and BP4 not met).
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	ℹ	✖	This variant received a total of 0.5 points in 1 proband. (PS4 not met; PMID: 22653678).
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	ℹ	✖	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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	ℹ	✖	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