

Variant: NM_000546.5(TP53):c.37C>T (p.Pro13Ser)

Version: 2.0

CA16616008 [↗](#)

406604 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: f7698bc5-923c-4132-b1b9-68a6bd158f1b

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HGVS expressions

NM_000546.5(TP53):c.37C>T (p.Pro13Ser)

NM_000546.5:c.37C>T

NC_000017.11:g.7676558G>A

CM000679.2:g.7676558G>A

NC_000017.10:g.7579876G>A

CM000679.1:g.7579876G>A

NC_000017.9:g.7520601G>A

NG_017013.2:g.15993C>T

ENST00000503591.2:c.37C>T

ENST00000508793.6:c.37C>T

ENST00000509690.6:c.-21-1322C>T

ENST00000514944.6:c.37C>T

ENST00000604348.6:c.37C>T

ENST00000269305.9:c.37C>T

ENST00000269305.8:c.37C>T

ENST00000359597.8:c.37C>T

ENST00000413465.6:c.37C>T

ENST00000420246.6:c.37C>T

ENST00000445888.6:c.37C>T

ENST00000455263.6:c.37C>T

ENST00000503591.1:c.37C>T

ENST00000505014.5:n.176C>T

ENST00000508793.5:c.37C>T

ENST00000509690.5:c.-21-1322C>T

ENST00000514944.5:c.37C>T

ENST00000604348.5:c.37C>T

ENST00000610292.4:c.-198C>T

ENST00000610538.4:c.-81C>T

ENST00000615910.4:c.37C>T

ENST00000617185.4:c.37C>T

ENST00000619485.4:c.-81C>T

ENST00000620739.4:c.-81C>T

ENST00000622645.4:c.-81C>T

ENST00000635293.1:c.-81C>T

NM_001126112.2:c.37C>T

NM_001126113.2:c.37C>T

NM_001126114.2:c.37C>T

NM_001126118.1:c.-198C>T
NM_001276695.1:c.-81C>T
NM_001276696.1:c.-81C>T
NM_001276760.1:c.-81C>T
NM_001276761.1:c.-81C>T
NM_001276695.2:c.-81C>T
NM_001276696.2:c.-81C>T
NM_001276760.2:c.-81C>T
NM_001276761.2:c.-81C>T
NM_000546.6:c.37C>T
NM_001126112.3:c.37C>T
NM_001126113.3:c.37C>T
NM_001126114.3:c.37C>T
NM_001126118.2:c.-198C>T
NM_001276695.3:c.-81C>T
NM_001276696.3:c.-81C>T
NM_001276760.3:c.-81C>T
NM_001276761.3:c.-81C>T

Uncertain Significance

Met criteria codes 6

- PS4_Moderate
- BS3
- BS2_Supporting
- BP4
- PP4
- PM2_Supporting

Not Met criteria codes 8

- BA1
- BS1
- PVS1
- PS1
- PS2
- PS3
- PP3
- 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(TP53):c.37C>T variant in TP53 is a missense variant predicted to cause substitution of proline by serine at amino acid 13 (p.Pro13Ser). This variant has been reported in 4 unrelated probands meeting Revised Chompret 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; 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 has been observed in 3 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_Supporting; Internal lab contributor). This variant has an allele frequency of 0.000001239 (2/1613918 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has a subpopulation allele frequency of <0.00004 in all non-bottleneck populations with 2 or more alleles present (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity by the majority of available assays indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 30224644). Computational predictor scores (BayesDel = 0.123287; 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). Although this variant meets the criteria to be classified as Likely Benign, the VCEP has overridden this classification to variant of uncertain significance for Li Fraumeni syndrome due to conflicting evidence: BS3, BP4, PM2_supporting, PS4_moderate, PP4, BS2_Supporting. (Bayesian Points: -2; VCEP specifications version 2.4)

Met criteria codes

PS4_Moderate			This variant has been reported in 4 unrelated probands meeting Revised Chompret 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; Internal lab contributors).
BS3			In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity by the majority of available assays indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 30224644).
BS2_Supporting			This variant has been observed in 3 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_Supporting; Internal lab contributor).
BP4			Computational predictor scores (BayesDel = 0.123287; 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).
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).
PM2_Supporting			This variant has an allele frequency of 0.000001239 (2/1613918 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has a subpopulation allele frequency of <0.00004 in all non-bottleneck populations with 2 or more alleles present (PM2_Supporting).

Not Met criteria codes

BA1			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
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

PP3			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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