

Variant: NM_000546.6(TP53):c.883C>T (p.Pro295Ser)

Version: 2.0

CA397836496 [↗](#)

428862 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 76e4a955-af29-4437-9e32-387b300c80d4

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HGVS expressions

NM_000546.6:c.883C>T

NM_000546.6(TP53):c.883C>T (p.Pro295Ser)

NC_000017.11:g.7673737G>A

CM000679.2:g.7673737G>A

NC_000017.10:g.7577055G>A

CM000679.1:g.7577055G>A

NC_000017.9:g.7517780G>A

NG_017013.2:g.18814C>T

ENST00000503591.2:c.883C>T

ENST00000508793.6:c.883C>T

ENST00000509690.6:c.487C>T

ENST00000514944.6:c.604C>T

ENST00000604348.6:c.862C>T

ENST00000269305.9:c.883C>T

ENST00000269305.8:c.883C>T

ENST00000359597.8:c.883C>T

ENST00000413465.6:c.782+444C>T

ENST00000420246.6:c.883C>T

ENST00000445888.6:c.883C>T

ENST00000455263.6:c.883C>T

ENST00000504290.5:c.487C>T

ENST00000504937.5:c.487C>T

ENST00000509690.5:c.487C>T

ENST00000510385.5:c.487C>T

ENST00000610292.4:c.766C>T

ENST00000610538.4:c.766C>T

ENST00000610623.4:c.406C>T

ENST00000615910.4:c.850C>T

ENST00000617185.4:c.883C>T

ENST00000618944.4:c.406C>T

ENST00000619186.4:c.406C>T

ENST00000619485.4:c.766C>T

ENST00000620739.4:c.766C>T

ENST00000622645.4:c.766C>T

ENST00000635293.1:c.766C>T

NM_000546.5:c.883C>T

NM_001126112.2:c.883C>T

NM_001126113.2:c.883C>T
NM_001126114.2:c.883C>T
NM_001126115.1:c.487C>T
NM_001126116.1:c.487C>T
NM_001126117.1:c.487C>T
NM_001126118.1:c.766C>T
NM_001276695.1:c.766C>T
NM_001276696.1:c.766C>T
NM_001276697.1:c.406C>T
NM_001276698.1:c.406C>T
NM_001276699.1:c.406C>T
NM_001276760.1:c.766C>T
NM_001276761.1:c.766C>T
NM_001276695.2:c.766C>T
NM_001276696.2:c.766C>T
NM_001276697.2:c.406C>T
NM_001276698.2:c.406C>T
NM_001276699.2:c.406C>T
NM_001276760.2:c.766C>T
NM_001276761.2:c.766C>T
NM_001126112.3:c.883C>T
NM_001126113.3:c.883C>T
NM_001126114.3:c.883C>T
NM_001126115.2:c.487C>T
NM_001126116.2:c.487C>T
NM_001126117.2:c.487C>T
NM_001126118.2:c.766C>T
NM_001276695.3:c.766C>T
NM_001276696.3:c.766C>T
NM_001276697.3:c.406C>T
NM_001276698.3:c.406C>T
NM_001276699.3:c.406C>T
NM_001276760.3:c.766C>T
NM_001276761.3:c.766C>T

Likely Benign

Met criteria codes 3

BS3 BP4 PM2_Supporting

Not Met criteria codes 17

BA1 BS2 BS1 BS4 PVS1
BP5 BP1 PS1 PS2 PS3 PS4
PP1 PP2 PP3 PP4 PM1
PM5

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 2.0.0

Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.883C>T variant in TP53 is a missense variant predicted to cause substitution of proline by serine at amino acid 295 (p.Pro295Ser). This variant has an allele frequency of 0.000004237 (5/1180042 alleles) in the European non-Finnish 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 functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 30224644). Computational predictor scores (BayesDel = -0.2; Align GVGD Class 0) are below the recommended thresholds (BayesDel ≤ -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_Moderate). 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_Moderate. (Bayesian Points: -5; VCEP specifications version 2.0; 7/24/2024)

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, 30224644).
BP4			BP4_MODERATE MET Computational predictor scores (BayesDel = -0.2; Align GVGD Class 0) are below the recommended thresholds (BayesDel ≤ -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_Moderate).
PM2_Supporting			This variant has an allele frequency of 0.000004237 (5/1180042 alleles) in the European non-Finnish 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).

Not Met criteria codes

BA1			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
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP1		✖	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
PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2		✖	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
PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5		✖	Another missense variant (c.884C>T, p.Pro295Leu) in the same codon has been reported(ClinVar Variation ID: 420974). However, this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP’s specifications (PM5 not met).

Curation History [↗](#)

