

Variant: *NM_000546.5(TP53):c.847C>T (p.Arg283Cys)*

Version: 2.1

[CA000457](#) 

[127824 \(ClinVar\)](#) 

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

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

Inheritance Mode: Autosomal dominant inheritance

UID: 0b9a7a17-b7b8-4223-bd64-69617a2d691d

Approved on: 2024-08-05

Published on: 2024-08-05

HGVS expressions

NM_000546.5:c.847C>T

NM_000546.5(TP53):c.847C>T (p.Arg283Cys)

NC_000017.11:g.7673773G>A

CM000679.2:g.7673773G>A

NC_000017.10:g.7577091G>A

CM000679.1:g.7577091G>A

NC_000017.9:g.7517816G>A

NG_017013.2:g.18778C>T

ENST00000503591.2:c.847C>T

ENST00000508793.6:c.847C>T

ENST00000509690.6:c.451C>T

ENST00000514944.6:c.568C>T

ENST00000604348.6:c.826C>T

ENST00000269305.9:c.847C>T

ENST00000269305.8:c.847C>T

ENST00000359597.8:c.847C>T

ENST00000413465.6:c.782+408C>T

ENST00000420246.6:c.847C>T

ENST00000445888.6:c.847C>T

ENST00000455263.6:c.847C>T

ENST00000504290.5:c.451C>T

ENST00000504937.5:c.451C>T

ENST00000509690.5:c.451C>T

ENST00000510385.5:c.451C>T

ENST00000610292.4:c.730C>T

ENST00000610538.4:c.730C>T

ENST00000610623.4:c.370C>T

ENST00000615910.4:c.814C>T

ENST00000617185.4:c.847C>T

ENST00000618944.4:c.370C>T

ENST00000619186.4:c.370C>T

ENST00000619485.4:c.730C>T

ENST00000620739.4:c.730C>T

ENST00000622645.4:c.730C>T

ENST00000635293.1:c.730C>T

NM_001126112.2:c.847C>T

NM_001126113.2:c.847C>T

NM_001126114.2:c.847C>T
NM_001126115.1:c.451C>T
NM_001126116.1:c.451C>T
NM_001126117.1:c.451C>T
NM_001126118.1:c.730C>T
NM_001276695.1:c.730C>T
NM_001276696.1:c.730C>T
NM_001276697.1:c.370C>T
NM_001276698.1:c.370C>T
NM_001276699.1:c.370C>T
NM_001276760.1:c.730C>T
NM_001276761.1:c.730C>T
NM_001276695.2:c.730C>T
NM_001276696.2:c.730C>T
NM_001276697.2:c.370C>T
NM_001276698.2:c.370C>T
NM_001276699.2:c.370C>T
NM_001276760.2:c.730C>T
NM_001276761.2:c.730C>T
NM_000546.6:c.847C>T
NM_001126112.3:c.847C>T
NM_001126113.3:c.847C>T
NM_001126114.3:c.847C>T
NM_001126115.2:c.451C>T
NM_001126116.2:c.451C>T
NM_001126117.2:c.451C>T
NM_001126118.2:c.730C>T
NM_001276695.3:c.730C>T
NM_001276696.3:c.730C>T
NM_001276697.3:c.370C>T
NM_001276698.3:c.370C>T
NM_001276699.3:c.370C>T
NM_001276760.3:c.730C>T
NM_001276761.3:c.730C>T

Likely Benign

Met criteria codes 4

PM5_Supporting PP3 BS2 BS3

Not Met criteria codes 15

PS1 PS2 PS3 PS4 BP4 BP2
BP5 PP1 PP4 PM2 PM1
PM3 BA1 PVS1 BS1

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.847C>T variant in TP53 is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 283(p.Arg283Cys). This variant has been observed in at least 8 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; SCV000183772.8). 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, 29979965, 30224644). Computational predictor scores (BayesDel = 0.33; Align GVGD = Class 55) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3). Another missense variant (c.848G>C, p.Arg283Pro) (ClinVar Variation ID: 486555), in the same codon have been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications. (PM5_Supporting). In summary, this variant meets the criteria to be classified as Likely Benign for Li Fraumeni Syndrome. Although there are both pathogenic and benign types of evidence for this variant, the pathogenic evidence is not considered inconsistent with the final classification. ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2, BS3, PP3, PM5_Supporting. (Bayesian Points: -6; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

| | | | |
|-----------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PM5_Supporting |  |  | Another missense variant (c.848G>C, p.Arg283Pro) (ClinVar Variation ID: 486555), in the same codon have been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications. (PM5_Supporting). |
| PP3 |  |  | Computational predictor scores (BayesDel = 0.33; Align GVGD = Class C55) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3). |
| BS2 |  |  | This variant has been observed in at least 8 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; SCV000183772.8). |
| 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, 29979965, 30224644). |

Not Met criteria codes

| | | | |
|------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 |  |  | This variant has been reported in 3 unrelated families meeting Revised Chompret criteria. Based on this evidence, this variant scores 1.5 total points meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; Internal lab contributor: SCV000183772.8). PS4 not applied as PM2_Supporting not applied. |

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| BP4 |  |  | 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 |
| BP5 | |  | This variant was found in one woman with breast cancer at 29 and ovarian cancer at 56 who also had a pathogenic variant in BRCA2, but this does not rule out the pathogenicity of this variant. |
| PP1 |  |  | 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 |
| PM2 | |  | The highest population minor allele frequency in gnomAD v41.0 is 0.00008559 (101/1180022 alleles) in the European (non-Finnish) population (PM2, BS1, and BA1 are not met). |
| 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). |
| PM3 | |  | 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 |
| PVS1 |  |  | 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 |

Curation History [↗](#)

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