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

BS3 BS2 PP3 PM5_Supporting

Not Met criteria codes 15

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

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

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).
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).
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).
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).

Not Met criteria codes

BS1	✖	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 pathogencity of this variant.
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
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
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.
BA1	✖	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
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

Curation History

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