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Variant: NM_000546.6(TP53):c.541C>T (p.Arg181Cys)

Version: 1.0

CA000257

142624 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 299d149c-670b-4c03-b78c-1368a1e93d27
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HGVS expressions

NM_000546.6:c.541C>T
NM_000546.6(TP53):c.541C>T (p.Arg181Cys)
NC_000017.11:g.7675071G>A
CM000679.2:g.7675071G>A
NC_000017.10:g.7578389G>A
CM000679.1:g.7578389G>A
NC_000017.9:g.7519114G>A
NG_017013.2:g.17480C>T
ENST00000503591.2:c.541C>T
ENST00000508793.6:c.541C>T
ENST00000509690.6:c.145C>T
ENST00000514944.6:c.262C>T
ENST00000604348.6:c.520C>T
ENST00000269305.9:c.541C>T
ENST00000269305.8:c.541C>T
ENST00000359597.8:c.541C>T
ENST00000413465.6:c.541C>T
ENST00000420246.6:c.541C>T
ENST00000445888.6:c.541C>T
ENST00000455263.6:c.541C>T
ENST00000504290.5:c.145C>T
ENST00000504937.5:c.145C>T
ENST00000505014.5:n.797C>T
ENST00000509690.5:c.145C>T
ENST00000510385.5:c.145C>T
ENST00000514944.5:c.262C>T
ENST00000574684.1:n.49C>T
ENST00000610292.4:c.424C>T
ENST00000610538.4:c.424C>T
ENST00000610623.4:c.64C>T
ENST00000615910.4:c.508C>T
ENST00000617185.4:c.541C>T
ENST00000618944.4:c.64C>T
ENST00000619186.4:c.64C>T
ENST00000619485.4:c.424C>T
ENST00000620739.4:c.424C>T
ENST00000622645.4:c.424C>T

ENST00000635293.1:c.424C>T
NM_000546.5:c.541C>T
NM_001126112.2:c.541C>T
NM_001126113.2:c.541C>T
NM_001126114.2:c.541C>T
NM_001126115.1:c.145C>T
NM_001126116.1:c.145C>T
NM_001126117.1:c.145C>T
NM_001126118.1:c.424C>T
NM_001276695.1:c.424C>T
NM_001276696.1:c.424C>T
NM_001276697.1:c.64C>T
NM_001276698.1:c.64C>T
NM_001276699.1:c.64C>T
NM_001276760.1:c.424C>T
NM_001276761.1:c.424C>T
NM_001276695.2:c.424C>T
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NM_001276699.2:c.64C>T
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NM_001126112.3:c.541C>T
NM_001126113.3:c.541C>T
NM_001126114.3:c.541C>T
NM_001126115.2:c.145C>T
NM_001126116.2:c.145C>T
NM_001126117.2:c.145C>T
NM_001126118.2:c.424C>T
NM_001276695.3:c.424C>T
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NM_001276697.3:c.64C>T
NM_001276698.3:c.64C>T
NM_001276699.3:c.64C>T
NM_001276760.3:c.424C>T
NM_001276761.3:c.424C>T

Likely Pathogenic

Met criteria codes 7

PP4_Moderate PM1_Supporting PP3_Moderate BS2 PM2_Supporting PS4 PP1

Not Met criteria codes 5

BS1 BS3 BP4 PS3 BA1

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 2.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.541C>T variant in TP53 is a missense variant predicted to cause substitution of Arginine by Cysteine at amino acid 181 (p.Arg181Cys). This variant has been reported in 10 unrelated families meeting Revised Chompret criteria and reported in 1 individuals under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 5.5 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMIDs: 1581912, 27866339, 28486781, 27501770, Internal contributors). The variant has been reported to segregate with LFS-associated cancers in 3-4 meioses in 2 families (PP1; PMID:28486781, Clinvar SCV000186999.12). At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, Internal lab contributor). 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; ClinVarSCV000186999.12, Internal lab contributor). This variant has an allele frequency of 0.000001859 (3/1614080 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 partially functional transactivation and retained growth suppression activity suggesting that this variant does not impact protein function; however, all assays did not agree (BS3_Supporting not met; PMIDs: 12826609, 30224644, 29979965, 39774325). This variant has 9 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspot by the Clingen TP53 VCEP (2-9 somatic occurrences, PMID: 30311369) (PM1_Supporting). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2, PS4, PP3_Moderate, PP4_Moderate, PP1, PM1_Supporting, PM2_Supporting. (Bayesian Points: 7; VCEP specifications version 2.3)

Met criteria codes

PP4_Moderate ✔	At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, Internal lab contributor).
PM1_Supporting ✔	This variant has 9 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspot by the Clingen TP53 VCEP (2-9 somatic occurrences, PMID: 30311369) (PM1_Supporting).
PP3_Moderate ✔	Computational predictor scores (BayesDel = 0.4693; Align GVGD = Class C65) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate).
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; ClinVarSCV000186999.12, Internal lab contributor).
PM2_Supporting ✔	This variant has an allele frequency of 0.000001859 (3/1614080 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).
PS4 ✔	This variant has been reported in 10 unrelated families meeting Revised Chompret criteria and reported in 1 individuals under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 5.5 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMIDs: 1581912, 27866339, 28486781, 27501770, Internal contributors).

PP1		✔	The variant has been reported to segregate with LFS-associated cancers in 3-4 meioses in 2 families (PP1; PMID:28486781, Clinvar SCV000186999.12).

Not Met criteria codes

BS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and retained growth suppression activity suggesting that this variant does not impact protein function; however, all assays did not agree (BS3_Supporting not met; PMIDs: 12826609, 30224644, 29979965, 39774325).
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and retained growth suppression activity suggesting that this variant does not impact protein function; however, all assays did not agree (BS3_Supporting not met; PMIDs: 12826609, 30224644, 29979965, 39774325).
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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