Variant: NM_000546.6(TP53):c.328C>T (p.Arg110Cys)

Version: 1.0

CA000119

142206 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8ac02151-a77e-465e-8fd3-da1ed8b14f5d
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HGVS expressions

NM_000546.6:c.328C>T
NM_000546.6(TP53):c.328C>T (p.Arg110Cys)
NC_000017.11:g.7676041G>A
CM000679.2:g.7676041G>A
NC_000017.10:g.7579359G>A
CM000679.1:g.7579359G>A
NC_000017.9:g.7520084G>A
NG_017013.2:g.16510C>T
ENST00000503591.2:c.328C>T
ENST00000508793.6:c.328C>T
ENST00000509690.6:c.-21-805C>T
ENST00000514944.6:c.96+341C>T
ENST00000604348.6:c.328C>T
ENST00000269305.9:c.328C>T
ENST00000269305.8:c.328C>T
ENST00000359597.8:c.328C>T
ENST00000413465.6:c.328C>T
ENST00000420246.6:c.328C>T
ENST00000445888.6:c.328C>T
ENST00000455263.6:c.328C>T
ENST00000503591.1:c.328C>T
ENST00000505014.5:n.584C>T
ENST00000508793.5:c.328C>T
ENST00000509690.5:c.-21-805C>T
ENST00000514944.5:c.96+341C>T
ENST00000604348.5:c.328C>T
ENST00000610292.4:c.211C>T
ENST00000610538.4:c.211C>T
ENST00000615910.4:c.328C>T
ENST00000617185.4:c.328C>T
ENST00000619485.4:c.211C>T
ENST00000620739.4:c.211C>T
ENST00000622645.4:c.211C>T
ENST00000635293.1:c.211C>T
NM_000546.5:c.328C>T
NM_001126112.2:c.328C>T
NM_001126113.2:c.328C>T

NM_001126114.2:c.328C>T
NM_001126118.1:c.211C>T
NM_001276695.1:c.211C>T
NM_001276696.1:c.211C>T
NM_001276760.1:c.211C>T
NM_001276761.1:c.211C>T
NM_001276695.2:c.211C>T
NM_001276696.2:c.211C>T
NM_001276760.2:c.211C>T
NM_001276761.2:c.211C>T
NM_001126112.3:c.328C>T
NM_001126113.3:c.328C>T
NM_001126114.3:c.328C>T
NM_001126118.2:c.211C>T
NM_001276695.3:c.211C>T
NM_001276696.3:c.211C>T
NM_001276760.3:c.211C>T
NM_001276761.3:c.211C>T

Uncertain Significance

Met criteria codes 6

BS2 BP4 PS4_Moderate PP4 PM1_Supporting PM2_Supporting

Not Met criteria codes 9

BS1 BS3 PS1 PS2 PS3 BA1 PP1 PP3 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 2.3.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.328C>T (p.Arg110Cys) variant in TP53 is a missense variant predicted to cause substitution of Arginine by Cysteine at amino acid 110 (p.Arg110Cys). This variant has been reported in 5 unrelated families meeting Revised Chompret criteria and one family meeting Classic criteria. Based on this evidence, this variant scores 3.5 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; Internal contributors). This variant has been observed in 4-7 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_Moderate; Internal lab contributor). 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 an allele frequency of 0.00001427 (23/1612280 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 conflicting results with respect to transactivation, growth suppression activity, and/or tetramer formation (PS3/BS3 not met; PMIDs: 12826609, 16007150, 29979965, 30224644). Computational predictor scores (BayesDel = 0.0367; Align GVGD Class C35) 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). This variant has 6 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 a variant of uncertain significance for Li Fraumeni syndrome based on the ACMG/AMP criteria

applied, as specified by the ClinGen TP53 VCEP: PS4_Moderate, PP4, BS2_Moderate, PM2_Supporting, BP4, PM1_Supporting. (Bayesian Points: 2; VCEP specifications version 2.3)

Met criteria codes

BS2	✔	BS2_MODERATE This variant has been observed in 4-7 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_Moderate; Internal lab contributor)
BP4	✔	Computational predictor scores (BayesDel = 0.0367; Align GVGD Class C35) 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).
PS4_Moderate	✔	This variant has been reported in 5 unrelated families meeting Revised Chompret criteria and one family meeting Classic criteria. Based on this evidence, this variant scores 3.5 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; Internal contributors).
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).
PM1_Supporting	✔	This variant has 6 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).
PM2_Supporting	✔	This variant has an allele frequency of 0.00001427 (23/1612280 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

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 conflicting results with respect to transactivation, growth suppression activity, and/or tetramer formation (PS3/BS3 not met; PMIDs: 12826609, 16007150, 29979965, 30224644)
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	✖	In vitro assays performed in yeast and/or human cell lines showed conflicting results with respect to transactivation, growth suppression activity, and/or tetramer formation (PS3/BS3 not met; PMIDs: 12826609, 16007150, 29979965,

30224644)

BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	ℹ	✖	2 different missense variants(c.329G>T, p.Arg110Leu and c.329G>C, p.Arg110Pro) (ClinVar Variation IDs: 406597, 233627), in the same codon have been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications, however, the functional data for these variants are pathogenic while functional evidence for the variant in question is benign. The VCEP overrode application of the code in this case.

Curation History

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