

Variant: NM_000546.6(TP53):c.329G>T (p.Arg110Leu)

Version: 1.0

CA002845 [↗](#)

406597 (ClinVar) [↗](#)

Gene: TP53 ([HGNC:7157](#))
Condition: Li-Fraumeni syndrome ([MONDO:0018875](#))
Inheritance Mode: Autosomal dominant inheritance
UUID: 1a754056-d029-4f44-9d93-a2908e659b57
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Published on: 2025/7/18

HGVS expressions

NM_000546.6(TP53):c.329G>T (p.Arg110Leu)
NM_000546.6:c.329G>T
NC_000017.11:g.7676040C>A
CM000679.2:g.7676040C>A
NC_000017.10:g.7579358C>A
CM000679.1:g.7579358C>A
NC_000017.9:g.7520083C>A
NG_017013.2:g.16511G>T
ENST00000503591.2:c.329G>T
ENST00000508793.6:c.329G>T
ENST00000509690.6:c.-21-804G>T
ENST00000514944.6:c.96+342G>T
ENST00000604348.6:c.329G>T
ENST00000269305.9:c.329G>T
ENST00000269305.8:c.329G>T
ENST00000359597.8:c.329G>T
ENST00000413465.6:c.329G>T
ENST00000420246.6:c.329G>T
ENST00000445888.6:c.329G>T
ENST00000455263.6:c.329G>T
ENST00000503591.1:c.329G>T
ENST00000505014.5:n.585G>T
ENST00000508793.5:c.329G>T
ENST00000509690.5:c.-21-804G>T
ENST00000514944.5:c.96+342G>T
ENST00000604348.5:c.329G>T
ENST00000610292.4:c.212G>T
ENST00000610538.4:c.212G>T
ENST00000615910.4:c.329G>T
ENST00000617185.4:c.329G>T
ENST00000619485.4:c.212G>T
ENST00000620739.4:c.212G>T
ENST00000622645.4:c.212G>T
ENST00000635293.1:c.212G>T
NM_000546.5:c.329G>T
NM_001126112.2:c.329G>T
NM_001126113.2:c.329G>T

NM_001126114.2:c.329G>T
NM_001126118.1:c.212G>T
NM_001276695.1:c.212G>T
NM_001276696.1:c.212G>T
NM_001276760.1:c.212G>T
NM_001276761.1:c.212G>T
NM_001276695.2:c.212G>T
NM_001276696.2:c.212G>T
NM_001276760.2:c.212G>T
NM_001276761.2:c.212G>T
NM_001126112.3:c.329G>T
NM_001126113.3:c.329G>T
NM_001126114.3:c.329G>T
NM_001126118.2:c.212G>T
NM_001276695.3:c.212G>T
NM_001276696.3:c.212G>T
NM_001276760.3:c.212G>T
NM_001276761.3:c.212G>T

Pathogenic

Met criteria codes 7

- PM2_Supporting
- PS2
- PS3
- PP1
- PP3
- PM1
- PS4_Supporting

Not Met criteria codes 10

- BS2
- BS1
- BS3
- BP4
- BP2
- BA1
- PS1
- PP4
- PM6
- 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.329G>T variant in TP53 is a missense variant predicted to cause substitution of arginine by leucine at amino acid 110 (p.Arg110Leu). 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; PMID: 30875412; Internal lab contributors). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with a strongly LFS-associated cancer totaling 4 phenotype points (PS2; Internal lab contributors). The variant has been reported to segregate with LFS-associated cancers in 3-4 meioses in 1 family (PP1; Internal contributors). This variant has an allele frequency of 0.000001240 (2/1612260 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 non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965). This variant has [XX] 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 (≥ 10 somatic occurrences, PMID: 30311369) (PM1). Computational predictor scores (BayesDel = 0.213246; Align GVGD = Class C25) 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). In summary, this variant meets the criteria to be classified as Pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS2, PS3, PM1, PP1, PP3, PM2_Supporting, PS4_Supporting. (Bayesian Points: 14; VCEP specifications version 2.3)

Met criteria codes

PM2_Supporting			This variant has an allele frequency of 0.000001240 (2/1612260 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).
PS2			This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with a strongly LFS-associated cancer totaling 4 phenotype points (PS2; Internal lab contributors).
PS3			In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965).
PP1			The variant has been reported to segregate with LFS-associated cancers in 3-4 meioses in 1 family (PP1; Internal contributors).
PP3			Computational predictor scores (BayesDel = 0.213246; Align GVGD = Class C25) 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).
PM1			This variant has [XX] 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 ($\geq$ 10 somatic occurrences, PMID: 30311369) (PM1).
PS4_Supporting			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; PMID: 30875412; Internal lab contributors).

Not Met criteria codes

BS2			One publication of a female proband with first cancer at 60+
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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

BA1			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
PP4			NA
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			5 different missense variants in the same codon have been reported (ClinVar Variation IDs:). However, these variants do not meet criteria for PM5 code application as they either curate to VUS/LB or have higher Grantham scores than the variant in question (PM5 not met).

Curation History 		
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