

Variant: NM_000546.6(TP53):c.329G>A (p.Arg110His)

Version: 1.1

CA000123 [↗](#)

127808 (ClinVar) [↗](#)

Gene: TP53 ([HGNC:7157](#))
Condition: Li-Fraumeni syndrome ([MONDO:0018875](#))
Inheritance Mode: Autosomal dominant inheritance
UUID: 00b45dfa-19f3-45de-975a-7b43bbc2be44
Approved on: 2025/1/16
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HGVS expressions

NM_000546.6(TP53):c.329G>A (p.Arg110His)
NM_000546.6:c.329G>A
NC_000017.11:g.7676040C>T
CM000679.2:g.7676040C>T
NC_000017.10:g.7579358C>T
CM000679.1:g.7579358C>T
NC_000017.9:g.7520083C>T
NG_017013.2:g.16511G>A
ENST00000503591.2:c.329G>A
ENST00000508793.6:c.329G>A
ENST00000509690.6:c.-21-804G>A
ENST00000514944.6:c.96+342G>A
ENST00000604348.6:c.329G>A
ENST00000269305.9:c.329G>A
ENST00000269305.8:c.329G>A
ENST00000359597.8:c.329G>A
ENST00000413465.6:c.329G>A
ENST00000420246.6:c.329G>A
ENST00000445888.6:c.329G>A
ENST00000455263.6:c.329G>A
ENST00000503591.1:c.329G>A
ENST00000505014.5:n.585G>A
ENST00000508793.5:c.329G>A
ENST00000509690.5:c.-21-804G>A
ENST00000514944.5:c.96+342G>A
ENST00000604348.5:c.329G>A
ENST00000610292.4:c.212G>A
ENST00000610538.4:c.212G>A
ENST00000615910.4:c.329G>A
ENST00000617185.4:c.329G>A
ENST00000619485.4:c.212G>A
ENST00000620739.4:c.212G>A
ENST00000622645.4:c.212G>A
ENST00000635293.1:c.212G>A
NM_000546.5:c.329G>A
NM_001126112.2:c.329G>A
NM_001126113.2:c.329G>A

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

Likely Benign

Met criteria codes 3

BS2 BP4 BS3_Supporting

Not Met criteria codes 14

BA1 BS1 BS4 BP5 BP2 PS1
PS2 PS3 PS4 PP1 PP3 PM1
PM5 PM2

Evidence Links 1

Expert Panel

TP53 VCEP

Criteria Specification Information

Criteria Specification: ClinGen TP53 Expert Panel
Specifications to the ACMG/AMP Variant Interpretation
Guidelines for TP53 Version 2.2.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.329G>A variant in TP53 is a missense variant predicted to cause substitution of arginine by histidine at amino acid 110 (p.Arg110His). 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 contributors). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00007119 (84/1,180,010 alleles) in the European (non-Finnish) population (PM2, BS1, and BA1 are not met). In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation, and retained growth suppression activity indicating that this variant does not impact protein function (BS3_Supporting; PMIDs: 12826609, 29979965, 30224644). Computational predictor scores (BayesDel = 0.0728; Align GVGD Class 0) 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). In summary, this variant meets the criteria to be classified as Likely Benign for Li Fraumeni syndrome. ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2_Moderate, BS3_Supporting, BP4. (Bayesian Points: -4; VCEP specifications version 2.1; 1/16/2025).

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 contributors).
BP4			Computational predictor scores (BayesDel = 0.0728; Align GVGD Class 0) 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).
BS3_Supporting			In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation, and retained growth suppression activity indicating that this variant does not impact protein function (BS3_Supporting; PMIDs: 12826609, 29979965, 30224644).
			Report a deleterious effect of this variant using a functional assay from patient blood sample. PubMed:33051313 
Not Met criteria codes			
BA1			The highest population minor allele frequency in gnomAD v4.1.0 is 0.00007119 (84/1,180,010 alleles) in the European (non-Finnish) population (PM2, BS1, and BA1 are not met).
BS1			The highest population minor allele frequency in gnomAD v4.1.0 is 0.00007119 (84/1,180,010 alleles) in the European (non-Finnish) population (PM2, BS1, and BA1 are not met).
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			These evidence codes are not currently applicable for TP53 VCEP curations
BP2			These evidence codes are not currently applicable for TP53 VCEP curations
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 1 proband meeting Revised Chompret criteria and in 1 individual under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 1 total point, meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. However, PS4 cannot be applied if PM2_Supporting is not met (PS4_not met; PMIDs: 23580068, Internal lab contributors).
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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).
PM5			5 different missense variants (c.329_330delinsCC (p.Arg110Pro); c.329G>C (p.Arg110Pro); c.329G>T (p.Arg110Leu); c.328C>G (p.Arg110Gly); c.328C>T (p.Arg110Cys)) in the same codon have been reported (ClinVar Variation IDs: 641505; 233627; 406597; 823452; 142206). However, these variants all have more damaging Grantham scores than the variant under consideration (PM5 not met). Grantham: R>H = 29 R>P = 103 R>L = 102 R>G = 125 R>C = 180 R>S = 110
PM2			The highest population minor allele frequency in gnomAD v4.1.0 is 0.00007119 (84/1,180,010 alleles) in the European (non-Finnish) population (PM2, BS1, and BA1 are not met).

Curation History 	
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