The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000546.6(TP53):c.523C>T (p.Arg175Cys)

Version: 1.3

CA002442

245851 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3699ed0e-e5f6-4457-bee4-961ef507dd2c
Approved on: 2026-01-06
Published on: 2026-01-14

HGVS expressions

NM_000546.6:c.523C>T
NM_000546.6(TP53):c.523C>T (p.Arg175Cys)
NC_000017.11:g.7675089G>A
CM000679.2:g.7675089G>A
NC_000017.10:g.7578407G>A
CM000679.1:g.7578407G>A
NC_000017.9:g.7519132G>A
NG_017013.2:g.17462C>T
ENST00000503591.2:c.523C>T
ENST00000508793.6:c.523C>T
ENST00000509690.6:c.127C>T
ENST00000514944.6:c.244C>T
ENST00000604348.6:c.502C>T
ENST00000269305.9:c.523C>T
ENST00000269305.8:c.523C>T
ENST00000359597.8:c.523C>T
ENST00000413465.6:c.523C>T
ENST00000420246.6:c.523C>T
ENST00000445888.6:c.523C>T
ENST00000455263.6:c.523C>T
ENST00000504290.5:c.127C>T
ENST00000504937.5:c.127C>T
ENST00000505014.5:n.779C>T
ENST00000509690.5:c.127C>T
ENST00000510385.5:c.127C>T
ENST00000514944.5:c.244C>T
ENST00000574684.1:n.31C>T
ENST00000610292.4:c.406C>T
ENST00000610538.4:c.406C>T
ENST00000610623.4:c.46C>T
ENST00000615910.4:c.490C>T
ENST00000617185.4:c.523C>T
ENST00000618944.4:c.46C>T
ENST00000619186.4:c.46C>T
ENST00000619485.4:c.406C>T
ENST00000620739.4:c.406C>T
ENST00000622645.4:c.406C>T

ENST00000635293.1:c.406C>T
NM_000546.5:c.523C>T
NM_001126112.2:c.523C>T
NM_001126113.2:c.523C>T
NM_001126114.2:c.523C>T
NM_001126115.1:c.127C>T
NM_001126116.1:c.127C>T
NM_001126117.1:c.127C>T
NM_001126118.1:c.406C>T
NM_001276695.1:c.406C>T
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NM_001276697.1:c.46C>T
NM_001276698.1:c.46C>T
NM_001276699.1:c.46C>T
NM_001276760.1:c.406C>T
NM_001276761.1:c.406C>T
NM_001276695.2:c.406C>T
NM_001276696.2:c.406C>T
NM_001276697.2:c.46C>T
NM_001276698.2:c.46C>T
NM_001276699.2:c.46C>T
NM_001276760.2:c.406C>T
NM_001276761.2:c.406C>T
NM_001126112.3:c.523C>T
NM_001126113.3:c.523C>T
NM_001126114.3:c.523C>T
NM_001126115.2:c.127C>T
NM_001126116.2:c.127C>T
NM_001126117.2:c.127C>T
NM_001126118.2:c.406C>T
NM_001276695.3:c.406C>T
NM_001276696.3:c.406C>T
NM_001276697.3:c.46C>T
NM_001276698.3:c.46C>T
NM_001276699.3:c.46C>T
NM_001276760.3:c.406C>T
NM_001276761.3:c.406C>T

Uncertain Significance

Met criteria codes 7

PS4_Moderate PP3_Moderate BS2 PM1 PM2_Supporting BS3_Supporting PP4_Moderate

Not Met criteria codes 13

BS1 BS4 BP7 BP4 BP2 PVS1 PM5 PS1 PS2 PS3 BA1 PM6 PP1

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 2.4.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.523C>T variant in TP53 is a missense variant predicted to cause substitution of arginine by cystindine at amino acid 175 (p.Arg175Cys). This variant has been reported in 4 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 2 total point meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMIDs: 40540701, 31119730; Internal lab contributors). This variant has an allele frequency of 0.00003293 (3/91090 alleles) in the South Asian population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_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). This variant resides within a codon (NM_00546.4: 175, 245, 248, 249, 273, 282) of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PM1; PMID: 8023157). Computational predictor scores (BayesDel = 0.5443; Align GVGD = Class 65) 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). 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: Ambry). 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: Invitae). Although this variant meets the criteria to be classified as Likely Pathogenic the VCEP has overridden the classification to variant of uncertain clinical significance due to ambiguous clinical data: PS4_Moderate, PM2_Supporting, BS3_Supporting, PM1, PP3_Moderate, BS2_Moderate, PP4_Moderate. (Bayesian Points: 6; VCEP specifications version 2.4)

Met criteria codes

PS4_Moderate ✔	This variant has been reported in 4 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 2 total point meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMIDs: 40540701, 31119730; Internal lab contributors).
PP3_Moderate ✔	Computational predictor scores (BayesDel = 0.5443; Align GVGD = Class 65) 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 ✔	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: Invitae).
PM1 ✔	This variant resides within a codon (NM_00546.4: 175, 245, 248, 249, 273, 282) of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PM1; PMID: 8023157).
PM2_Supporting ✔	This variant has an allele frequency of 0.00003293 (3/91090 alleles) in the South Asian population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
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).
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: Invitae).

Not Met criteria codes

BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	Variant is not synonymous
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	✖	Variant is not a null variant
PM5	✖	Code not applied as this variant has benign functional data and the other residues being compared have pathogenic functional data. This indicates this variant does not have the same impact as these other residues. 2 different missense variants (p.Arg175His and p.Arg175Gly) (ClinVar Variation ID: 12374, 376649), in the same codon have been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications. (PM5_Strong).
PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	✖	No enough evidence
PS3	✖	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
PM6	✖	No enough evidence
PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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