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.524G>T (p.Arg175Leu)

Version: 1.0

CA000252

182963 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 6aa7e5db-edd6-4608-a046-e82aa9ea21df
Approved on: 2024/9/6
Published on: 2024/9/6

HGVS expressions

NM_000546.6:c.524G>T
NM_000546.6(TP53):c.524G>T (p.Arg175Leu)
NC_000017.11:g.7675088C>A
CM000679.2:g.7675088C>A
NC_000017.10:g.7578406C>A
CM000679.1:g.7578406C>A
NC_000017.9:g.7519131C>A
NG_017013.2:g.17463G>T
ENST00000503591.2:c.524G>T
ENST00000508793.6:c.524G>T
ENST00000509690.6:c.128G>T
ENST00000514944.6:c.245G>T
ENST00000604348.6:c.503G>T
ENST00000269305.9:c.524G>T
ENST00000269305.8:c.524G>T
ENST00000359597.8:c.524G>T
ENST00000413465.6:c.524G>T
ENST00000420246.6:c.524G>T
ENST00000445888.6:c.524G>T
ENST00000455263.6:c.524G>T
ENST00000504290.5:c.128G>T
ENST00000504937.5:c.128G>T
ENST00000505014.5:n.780G>T
ENST00000509690.5:c.128G>T
ENST00000510385.5:c.128G>T
ENST00000514944.5:c.245G>T
ENST00000574684.1:n.32G>T
ENST00000610292.4:c.407G>T
ENST00000610538.4:c.407G>T
ENST00000610623.4:c.47G>T
ENST00000615910.4:c.491G>T
ENST00000617185.4:c.524G>T
ENST00000618944.4:c.47G>T
ENST00000619186.4:c.47G>T
ENST00000619485.4:c.407G>T
ENST00000620739.4:c.407G>T
ENST00000622645.4:c.407G>T

ENST00000635293.1:c.407G>T
NM_000546.5:c.524G>T
NM_001126112.2:c.524G>T
NM_001126113.2:c.524G>T
NM_001126114.2:c.524G>T
NM_001126115.1:c.128G>T
NM_001126116.1:c.128G>T
NM_001126117.1:c.128G>T
NM_001126118.1:c.407G>T
NM_001276695.1:c.407G>T
NM_001276696.1:c.407G>T
NM_001276697.1:c.47G>T
NM_001276698.1:c.47G>T
NM_001276699.1:c.47G>T
NM_001276760.1:c.407G>T
NM_001276761.1:c.407G>T
NM_001276695.2:c.407G>T
NM_001276696.2:c.407G>T
NM_001276697.2:c.47G>T
NM_001276698.2:c.47G>T
NM_001276699.2:c.47G>T
NM_001276760.2:c.407G>T
NM_001276761.2:c.407G>T
NM_001126112.3:c.524G>T
NM_001126113.3:c.524G>T
NM_001126114.3:c.524G>T
NM_001126115.2:c.128G>T
NM_001126116.2:c.128G>T
NM_001126117.2:c.128G>T
NM_001126118.2:c.407G>T
NM_001276695.3:c.407G>T
NM_001276696.3:c.407G>T
NM_001276697.3:c.47G>T
NM_001276698.3:c.47G>T
NM_001276699.3:c.47G>T
NM_001276760.3:c.407G>T
NM_001276761.3:c.407G>T

Likely Pathogenic

Met criteria codes 7

BS3_Supporting PS4_Moderate PP3_Moderate PM1 PM5 PM2_Supporting PP4

Not Met criteria codes 8

BA1 BS2 BS1 BP4 PS1 PS2 PS3 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 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.524G>T variant in TP53 is a missense variant predicted to cause substitution of arginine by leucine at amino acid 175 (p.Arg175Leu). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in 4 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 2 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMID: 16707427; Internal lab contributors: Invitae, Ambry). 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 = 0.57303; 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). At least one individual with this variant was found to have a variant allele fraction of ≤35%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, Internal lab contributor: Invitae). 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). Another missense variant(c.524G>A, p.Arg175His) (ClinVar Variation ID: 12374), in the same codon has been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications. (PM5). 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: PS4_Moderate, PM2_Supporting, BS3_Supporting, PP3_Moderate, PP4, PM1, PM5 (Bayesian Points: 9; VCEP specifications version 2.0; 9/6/2024)

Met criteria codes

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,).
PS4_Moderate ✔	This variant has been reported in 4 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 2 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMID: 16707427; Internal lab contributors: Invitae, Ambry).
PP3_Moderate ✔	Computational predictor scores (BayesDel = 0.57303; 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).
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).
PM5 ✔	Another missense variant(c.524G>A, p.Arg175His) (ClinVar Variation ID: 12374), in the same codon has been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications. (PM5).
PM2_Supporting ✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP4 ✔	At least one individual with this variant was found to have a variant allele fraction of ≤35%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, Internal lab contributor: Invitae).

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	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
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
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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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.6(TP53):c.524G>T (p.Arg1…	Likely Pathogenic	Li-Fraumeni Syndrome	2024-09-06	1.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0	TP53

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