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>A (p.Arg175His)

Version: 1.0

CA000251

12374 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 7447e408-66fd-43ee-8fc8-6012f43d7ada
Approved on: 2024/9/6
Published on: 2024/9/6

HGVS expressions

NM_000546.6:c.524G>A
NM_000546.6(TP53):c.524G>A (p.Arg175His)
NC_000017.11:g.7675088C>T
CM000679.2:g.7675088C>T
NC_000017.10:g.7578406C>T
CM000679.1:g.7578406C>T
NC_000017.9:g.7519131C>T
NG_017013.2:g.17463G>A
ENST00000503591.2:c.524G>A
ENST00000508793.6:c.524G>A
ENST00000509690.6:c.128G>A
ENST00000514944.6:c.245G>A
ENST00000604348.6:c.503G>A
ENST00000269305.9:c.524G>A
ENST00000269305.8:c.524G>A
ENST00000359597.8:c.524G>A
ENST00000413465.6:c.524G>A
ENST00000420246.6:c.524G>A
ENST00000445888.6:c.524G>A
ENST00000455263.6:c.524G>A
ENST00000504290.5:c.128G>A
ENST00000504937.5:c.128G>A
ENST00000505014.5:n.780G>A
ENST00000509690.5:c.128G>A
ENST00000510385.5:c.128G>A
ENST00000514944.5:c.245G>A
ENST00000574684.1:n.32G>A
ENST00000610292.4:c.407G>A
ENST00000610538.4:c.407G>A
ENST00000610623.4:c.47G>A
ENST00000615910.4:c.491G>A
ENST00000617185.4:c.524G>A
ENST00000618944.4:c.47G>A
ENST00000619186.4:c.47G>A
ENST00000619485.4:c.407G>A
ENST00000620739.4:c.407G>A
ENST00000622645.4:c.407G>A

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

Pathogenic

Met criteria codes 6

PM1 PP1_Moderate PS4_Moderate PS3 PP3 PM2_Supporting

Not Met criteria codes 9

PM5 BA1 BS2 BS1 BS4 BS3 BP4 PS1 PP4

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>A variant in TP53 is a missense variant predicted to cause substitution of arginine by histidine at amino acid 175 (p.Arg175His). This variant has been reported in 3 unrelated families meeting Classic and Revised Chompret criteria.Based on this evidence, this variant scores 2.5 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate: 8825920, 11370630, 8164043). The variant has been reported to segregate with LFS-associated cancers in 5-6 meioses in 1 family (PP1_Moderate; PMID: 8825920). 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 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 = 0.54619; 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). This variant has an allele frequency of 0.000005932 (7/1180032 alleles) in the European (non-Finnish) 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 summary, this variant meets the criteria to be classified as [CLASSIFICATION] for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS3, PP1_Moderate, PM1, PS4_Moderate, PP3, PM2_Supporting. (Bayesian Points: 12; VCEP specifications version 2.0; 9/6/2024)

Met criteria codes

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).
PP1_Moderate	✔	The variant has been reported to segregate with LFS-associated cancers in 5-6 meioses in 1 family (PP1_Moderate; PMID: 8825920).
PS4_Moderate	✔	This variant has been reported in 3 unrelated families meeting Classic and Revised Chompret criteria.Based on this evidence, this variant scores 2.5 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate: 8825920, 11370630, 8164043).
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).
PP3	✔	Computational predictor scores (BayesDel = 0.54619; 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).
PM2_Supporting	✔	This variant has an allele frequency of 0.000005932 (7/1180032 alleles) in the European (non-Finnish) 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).

Not Met criteria codes

PM5	✖	Other residues have worse Grantham scores than this variant

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
BS4		✖	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
PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.