

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: 2024-09-06

Published on: 2024-09-06

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

PP1_Moderate PS4_Moderate PS3
PP3 PM2_Supporting PM1

Not Met criteria codes 9

BA1 BS2 BS4 BS3 BS1 BP4
PS1 PP4 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 2.0.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

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

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).
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).

Not Met criteria codes

BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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BS2			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
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
PP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			Other residues have worse Grantham scores than this variant

Curation History 	
 Showing 1 to 1 of 1 rows	

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