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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(TP53):c.524G>A (p.Arg175His)
NM_000546.6:c.524G>A
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
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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
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NM_001276761.2:c.407G>A
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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

PS3 PP3 PM1 PP1_Moderate PS4_Moderate PM2_Supporting

Not Met criteria codes 9

PS1 PP4 PM5 BA1 BS1 BS4 BS3 BS2 BP4

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

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).
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).
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

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

PP4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	ℹ	✖	Other residues have worse Grantham scores than this variant
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	ℹ	✖	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 ℹ	Condition	Published Date	Version ℹ	Criteria Specification	Gene
View	NM_000546.6(TP53):c.524G>A (p.Arg1...	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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