

Variant: *NM_000546.6(TP53):c.1135C>A (p.Arg379Ser)*

Version: 2.0

CA000042 [↗](#)

186762 (ClinVar) [↗](#)

Gene: TP53 ([HGNC:7157](#))

Condition: Li-Fraumeni syndrome ([MONDO:0018875](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: ec12077e-ef5b-47b0-9426-2498d4b97853

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HGVS expressions

NM_000546.6:c.1135C>A

NM_000546.6(TP53):c.1135C>A (p.Arg379Ser)

NC_000017.11:g.7669656G>T

CM000679.2:g.7669656G>T

NC_000017.10:g.7572974G>T

CM000679.1:g.7572974G>T

NC_000017.9:g.7513699G>T

NG_017013.2:g.22895C>A

ENST00000503591.2:c.1135C>A

ENST00000508793.6:c.1135C>A

ENST00000509690.6:c.739C>A

ENST00000514944.6:c.856C>A

ENST00000604348.6:c.1114C>A

ENST00000269305.9:c.1135C>A

ENST00000269305.8:c.1135C>A

ENST00000359597.8:c.994-3412C>A

ENST00000413465.6:c.782+4525C>A

ENST00000420246.6:c.*242C>A

ENST00000445888.6:c.1135C>A

ENST00000455263.6:c.*154C>A

ENST00000504290.5:c.*154C>A

ENST00000504937.5:c.739C>A

ENST00000510385.5:c.*242C>A

ENST00000576024.1:c.88C>A

ENST00000610292.4:c.1018C>A

ENST00000610538.4:c.*154C>A

ENST00000610623.4:c.*154C>A

ENST00000615910.4:c.1102C>A

ENST00000617185.4:c.*242C>A

ENST00000618944.4:c.*242C>A

ENST00000619186.4:c.658C>A

ENST00000619485.4:c.1018C>A

ENST00000620739.4:c.1018C>A

ENST00000622645.4:c.*242C>A

ENST00000635293.1:c.983+953C>A

NM_000546.5:c.1135C>A

NM_001126112.2:c.1135C>A

NM_001126113.2:c.*154C>A
NM_001126114.2:c.*242C>A
NM_001126115.1:c.739C>A
NM_001126116.1:c.*242C>A
NM_001126117.1:c.*154C>A
NM_001126118.1:c.1018C>A
NM_001276695.1:c.*154C>A
NM_001276696.1:c.*242C>A
NM_001276697.1:c.658C>A
NM_001276698.1:c.*242C>A
NM_001276699.1:c.*154C>A
NM_001276760.1:c.1018C>A
NM_001276761.1:c.1018C>A
NM_001276695.2:c.*154C>A
NM_001276696.2:c.*242C>A
NM_001276697.2:c.658C>A
NM_001276698.2:c.*242C>A
NM_001276699.2:c.*154C>A
NM_001276760.2:c.1018C>A
NM_001276761.2:c.1018C>A
NM_001126112.3:c.1135C>A
NM_001126113.3:c.*154C>A
NM_001126114.3:c.*242C>A
NM_001126115.2:c.739C>A
NM_001126116.2:c.*242C>A
NM_001126117.2:c.*154C>A
NM_001126118.2:c.1018C>A
NM_001276695.3:c.*154C>A
NM_001276696.3:c.*242C>A
NM_001276697.3:c.658C>A
NM_001276698.3:c.*242C>A
NM_001276699.3:c.*154C>A
NM_001276760.3:c.1018C>A
NM_001276761.3:c.1018C>A

Likely Benign

Met criteria codes 4

- BS2
- BP4
- PS4_Supporting
- PM2_Supporting

Not Met criteria codes 12

- PM1
- PM5
- BS1
- BS4
- BS3
- PS1
- PS2
- PS3
- BA1
- PP1
- PP3
- 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.1135C>A variant in TP53 is a missense variant predicted to cause substitution of argine by serine at amino acid 379 (p.Arg379Ser). This variant has been observed in at least 8 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; Internal lab contributor: Invitae). This variant has been reported in 1 proband meeting Revised Chompret criteria and is reported in 1 individual under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 1 total point meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; Internal lab contributors: Invitae, GeneDx). This variant has an allele frequency of 0.000005932 (7/1179994 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). Computational predictor scores (BayesDel = -0.1497; Align GVGD Class C0) are below the recommended thresholds (BayesDel $\leq$ -0.008 and an Align GVGD Class $\leq$ 55), evidence that does not predict a damaging effect on TP53 via protein change. SpliceAI predicts that the variant has no impact on splicing. (BP4_Moderate). In summary, this variant meets the criteria to be classified as Likely Benign for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2, PS4_Supporting, PM2_Supporting, BS4_Moderate. (Bayesian Points: -4; VCEP specifications version 2.1; 1/16/2025)

Met criteria codes

BS2			This variant has been observed in at least 8 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; Internal lab contributor: Invitae).
BP4			BP4_MODERATE. Computational predictor scores (BayesDel = -0.1497; Align GVGD Class C0) are below the recommended thresholds (BayesDel $\leq$ -0.008 and an Align GVGD Class $\leq$ 55), evidence that does not predict a damaging effect on TP53 via protein change. SpliceAI predicts that the variant has no impact on splicing. (BP4_Moderate).
PS4_Supporting			This variant has been reported in 1 proband meeting Revised Chompret criteria and is reported in 1 individual under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 1 total point meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; Internal lab contributors: Invitae, GeneDx).
PM2_Supporting			This variant has an allele frequency of 0.000005932 (7/1179994 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

PM1			This variant does not reside within a region of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PM1 not met).
PM5			3 different missense variants (p.Arg379His, p.Arg379Leu, p.Arg379Cys) in the same codon have been reported. However, these variants have not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP’s specifications (PM5 not met).
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			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; however a third assay corroborating these findings was not available (BS3 not met; PMIDs: 12826609, 30224644).
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			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; however a third assay corroborating these findings was not available (BS3 not met; PMIDs: 12826609, 30224644).
BA1			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
PP3			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 [↗](#)



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