

Variant: NM_001126112.2(TP53):c.469G>A (p.Val157Ile)

Version: 2.0

CA000220 [↗](#)

185404 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: e2f03976-a476-46c6-bca8-f58d4a9373f3

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HGVS expressions

NM_001126112.2(TP53):c.469G>A (p.Val157Ile)

NM_001126112.2:c.469G>A

NC_000017.11:g.7675143C>T

CM000679.2:g.7675143C>T

NC_000017.10:g.7578461C>T

CM000679.1:g.7578461C>T

NC_000017.9:g.7519186C>T

NG_017013.2:g.17408G>A

ENST00000503591.2:c.469G>A

ENST00000508793.6:c.469G>A

ENST00000509690.6:c.73G>A

ENST00000514944.6:c.190G>A

ENST00000604348.6:c.448G>A

ENST00000269305.9:c.469G>A

ENST00000269305.8:c.469G>A

ENST00000359597.8:c.469G>A

ENST00000413465.6:c.469G>A

ENST00000420246.6:c.469G>A

ENST00000445888.6:c.469G>A

ENST00000455263.6:c.469G>A

ENST00000504290.5:c.73G>A

ENST00000504937.5:c.73G>A

ENST00000505014.5:n.725G>A

ENST00000508793.5:c.469G>A

ENST00000509690.5:c.73G>A

ENST00000510385.5:c.73G>A

ENST00000514944.5:c.190G>A

ENST00000610292.4:c.352G>A

ENST00000610538.4:c.352G>A

ENST00000610623.4:c.-9G>A

ENST00000615910.4:c.436G>A

ENST00000617185.4:c.469G>A

ENST00000618944.4:c.-9G>A

ENST00000619186.4:c.-9G>A

ENST00000619485.4:c.352G>A

ENST00000620739.4:c.352G>A

ENST00000622645.4:c.352G>A

ENST00000635293.1:c.352G>A

NM_000546.5:c.469G>A

NM_001126113.2:c.469G>A

NM_001126114.2:c.469G>A

NM_001126115.1:c.73G>A

NM_001126116.1:c.73G>A

NM_001126117.1:c.73G>A

NM_001126118.1:c.352G>A

NM_001276695.1:c.352G>A

NM_001276696.1:c.352G>A

NM_001276697.1:c.-9G>A

NM_001276698.1:c.-9G>A

NM_001276699.1:c.-9G>A

NM_001276760.1:c.352G>A

NM_001276761.1:c.352G>A

NM_001276695.2:c.352G>A

NM_001276696.2:c.352G>A

NM_001276697.2:c.-9G>A

NM_001276698.2:c.-9G>A

NM_001276699.2:c.-9G>A

NM_001276760.2:c.352G>A

NM_001276761.2:c.352G>A

NM_000546.6:c.469G>A

NM_001126112.3:c.469G>A

NM_001126113.3:c.469G>A

NM_001126114.3:c.469G>A

NM_001126115.2:c.73G>A

NM_001126116.2:c.73G>A

NM_001126117.2:c.73G>A

NM_001126118.2:c.352G>A

NM_001276695.3:c.352G>A

NM_001276696.3:c.352G>A

NM_001276697.3:c.-9G>A

NM_001276698.3:c.-9G>A

NM_001276699.3:c.-9G>A

NM_001276760.3:c.352G>A

NM_001276761.3:c.352G>A

Likely Benign

Met criteria codes 3

BS3_Supporting

BP4

BS2_Supporting

Not Met criteria codes 13

BS1

BS4

PS1

PS2

PS3

PS4

BA1

PP1

PP3

PP4

PM2

PM1

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 2.2.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

TP53 VCEP

The NM_000546.6:c.469G>A variant in TP53 is a missense variant predicted to cause substitution of valine by isoleucine at amino acid 157 (p.Val157Ile). This variant has been observed in at least 2 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_Supporting; Internal 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 = -0.057; 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_supporting, BS3_supporting, BP4_Moderate. (Bayesian Points: -4; VCEP specifications version 2.0, 1/16/2025).

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).
BP4			BP4_MODERATE Computational predictor scores (BayesDel = -0.057; 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).
BS2_Supporting			This variant has been observed in 2 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_Supporting; Invitae, Internal lab contributors).

Not Met criteria codes

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
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
PS4			Reported in several literature reports and IARC database; none that clearly meet Chompret or Classical LFS criteria

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
PM2		✖	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00006666 (4/60004 alleles) in the Admixed population (PM2, BS1, and BA1 are not met).
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		✖	5 different missense variants (p.Val157Gly, Val157Asp, p.Val157Ala, Val157Leu, Val157Phe) 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).

Curation History 		
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Showing 1 to 2 of 2 rows		

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