Variant: NM_001126112.2(TP53):c.998G>A (p.Arg333His)

Version: 2.0

CA000533

142273 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: d8de06fc-22f0-4978-9c21-a8d7b365d2c9
Approved on: 2025-03-04
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HGVS expressions

NM_001126112.2:c.998G>A
NM_001126112.2(TP53):c.998G>A (p.Arg333His)
NC_000017.11:g.7670711C>T
CM000679.2:g.7670711C>T
NC_000017.10:g.7574029C>T
CM000679.1:g.7574029C>T
NC_000017.9:g.7514754C>T
NG_017013.2:g.21840G>A
ENST00000503591.2:c.998G>A
ENST00000508793.6:c.998G>A
ENST00000509690.6:c.602G>A
ENST00000514944.6:c.719G>A
ENST00000604348.6:c.977G>A
ENST00000269305.9:c.998G>A
ENST00000269305.8:c.998G>A
ENST00000359597.8:c.993+2824G>A
ENST00000413465.6:c.782+3470G>A
ENST00000420246.6:c.*105G>A
ENST00000445888.6:c.998G>A
ENST00000455263.6:c.*17G>A
ENST00000504290.5:c.*17G>A
ENST00000504937.5:c.602G>A
ENST00000510385.5:c.*105G>A
ENST00000576024.1:c.54-1021G>A
ENST00000610292.4:c.881G>A
ENST00000610538.4:c.*17G>A
ENST00000610623.4:c.*17G>A
ENST00000615910.4:c.965G>A
ENST00000617185.4:c.*105G>A
ENST00000618944.4:c.*105G>A
ENST00000619186.4:c.521G>A
ENST00000619485.4:c.881G>A
ENST00000620739.4:c.881G>A
ENST00000622645.4:c.*105G>A
ENST00000635293.1:c.881G>A
NM_000546.5:c.998G>A
NM_001126113.2:c.*17G>A

NM_001126114.2:c.*105G>A
NM_001126115.1:c.602G>A
NM_001126116.1:c.*105G>A
NM_001126117.1:c.*17G>A
NM_001126118.1:c.881G>A
NM_001276695.1:c.*17G>A
NM_001276696.1:c.*105G>A
NM_001276697.1:c.521G>A
NM_001276698.1:c.*105G>A
NM_001276699.1:c.*17G>A
NM_001276760.1:c.881G>A
NM_001276761.1:c.881G>A
NM_001276695.2:c.*17G>A
NM_001276696.2:c.*105G>A
NM_001276697.2:c.521G>A
NM_001276698.2:c.*105G>A
NM_001276699.2:c.*17G>A
NM_001276760.2:c.881G>A
NM_001276761.2:c.881G>A
NM_000546.6:c.998G>A
NM_001126112.3:c.998G>A
NM_001126113.3:c.*17G>A
NM_001126114.3:c.*105G>A
NM_001126115.2:c.602G>A
NM_001126116.2:c.*105G>A
NM_001126117.2:c.*17G>A
NM_001126118.2:c.881G>A
NM_001276695.3:c.*17G>A
NM_001276696.3:c.*105G>A
NM_001276697.3:c.521G>A
NM_001276698.3:c.*105G>A
NM_001276699.3:c.*17G>A
NM_001276760.3:c.881G>A
NM_001276761.3:c.881G>A

Benign

Met criteria codes 3

BP4 BS3 BS2

Not Met criteria codes 12

BS1 BS4 PP1 PP3 PS1 PS2 PS3 PS4 BA1 PM1 PM5 PM2

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 2.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.998G>A variant in TP53 is a missense variant predicted to cause substitution of arginine by histidine at amino acid 333 (p.Arg333His). This variant has been observed in 4-7 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_Moderate; ClinVar SCVs: SCV000285219.10). In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 29979965, 30224644). Computational predictor scores (BayesDel = -0.0924; Align GVGD Class C0) are below the recommended thresholds (BayesDel ≤ -0.008 and an Align GVGD Class ≤ 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 benign for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2_Moderate, BS3, BP4_Moderate. (Bayesian Points: -8; VCEP specifications version 2.3; 3/4/2025).

Met criteria codes

BP4	✔	MODERATE. Computational predictor scores (BayesDel = -0.0924; Align GVGD Class C0) are below the recommended thresholds (BayesDel ≤ -0.008 and an Align GVGD Class ≤ 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).
BS3	✔	In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function(BS3; PMIDs: 12826609, 29979965, 30224644).
BS2	✔	MODERATE. This variant has been observed in 4-7 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_Moderate; ClinVar SCVs: SCV000285219.10).

Not Met criteria codes

BS1	✖	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00008789 (8/91026 alleles) in the South Asian population (PM2, BS1, and BA1 are not met).
BS4	✖	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
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		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1		✖	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00008789 (8/91026 alleles) in the South Asian 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		✖	Another missense variant (c.997C>T, p.Arg333Cys) in the same codon has been reported (ClinVar Variation ID: 184745). However, the variants have not yet been curated to determine if they would be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PM5 not evaluated).
PM2		✖	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00008789 (8/91026 alleles) in the South Asian population (PM2, BS1, and BA1 are not met).

Curation History

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