

Variant: *NM_000546.5(TP53):c.1025G>A (p.Arg342Gln)*

Version: 2.0

CA000835 [↗](#)

233136 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 7d33e69e-ea2d-4b37-aec4-486ba5df33e4

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HGVS expressions

NM_000546.5(TP53):c.1025G>A (p.Arg342Gln)

NM_000546.5:c.1025G>A

NC_000017.11:g.7670684C>T

CM000679.2:g.7670684C>T

NC_000017.10:g.7574002C>T

CM000679.1:g.7574002C>T

NC_000017.9:g.7514727C>T

NG_017013.2:g.21867G>A

ENST00000503591.2:c.1025G>A

ENST00000508793.6:c.1025G>A

ENST00000509690.6:c.629G>A

ENST00000514944.6:c.746G>A

ENST00000604348.6:c.1004G>A

ENST00000269305.9:c.1025G>A

ENST00000269305.8:c.1025G>A

ENST00000359597.8:c.993+2851G>A

ENST00000413465.6:c.782+3497G>A

ENST00000420246.6:c.*132G>A

ENST00000445888.6:c.1025G>A

ENST00000455263.6:c.*44G>A

ENST00000504290.5:c.*44G>A

ENST00000504937.5:c.629G>A

ENST00000510385.5:c.*132G>A

ENST00000576024.1:c.54-994G>A

ENST00000610292.4:c.908G>A

ENST00000610538.4:c.*44G>A

ENST00000610623.4:c.*44G>A

ENST00000615910.4:c.992G>A

ENST00000617185.4:c.*132G>A

ENST00000618944.4:c.*132G>A

ENST00000619186.4:c.548G>A

ENST00000619485.4:c.908G>A

ENST00000620739.4:c.908G>A

ENST00000622645.4:c.*132G>A

ENST00000635293.1:c.908G>A

NM_001126112.2:c.1025G>A

NM_001126113.2:c.*44G>A

	NM_001126114.2:c.*132G>A NM_001126115.1:c.629G>A NM_001126116.1:c.*132G>A NM_001126117.1:c.*44G>A NM_001126118.1:c.908G>A NM_001276695.1:c.*44G>A NM_001276696.1:c.*132G>A NM_001276697.1:c.548G>A NM_001276698.1:c.*132G>A NM_001276699.1:c.*44G>A NM_001276760.1:c.908G>A NM_001276761.1:c.908G>A NM_001276695.2:c.*44G>A NM_001276696.2:c.*132G>A NM_001276697.2:c.548G>A NM_001276698.2:c.*132G>A NM_001276699.2:c.*44G>A NM_001276760.2:c.908G>A NM_001276761.2:c.908G>A NM_000546.6:c.1025G>A NM_001126112.3:c.1025G>A NM_001126113.3:c.*44G>A NM_001126114.3:c.*132G>A NM_001126115.2:c.629G>A NM_001126116.2:c.*132G>A NM_001126117.2:c.*44G>A NM_001126118.2:c.908G>A NM_001276695.3:c.*44G>A NM_001276696.3:c.*132G>A NM_001276697.3:c.548G>A NM_001276698.3:c.*132G>A NM_001276699.3:c.*44G>A NM_001276760.3:c.908G>A NM_001276761.3:c.908G>A
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Likely Benign

Met criteria codes 4

BP4PM2_SupportingBS3BS2_Supporting

Not Met criteria codes 13

BA1BS1BS4PP1PP3PP4PS1PS2PS3PS4PM1PM5PM4

Evidence Links 2

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.1025G>A variant in TP53 is a missense variant predicted to cause substitution of arginine by glutamine at amino acid 342 (p.Arg342Gln). 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). This variant has been observed in 2-3 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; SCV000277448.6). Computational predictor scores (BayesDel =-0.2779; 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). This variant has an allele frequency of 0.000006780 (8/1180002 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 Likely Benign for Li Fraumeni syndrome. ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS3, BS2_Supporting, BP4_Moderate, PM2_Supporting. (Bayesian Points: -6; VCEP specifications version 2.0; 9/6/2024)

Met criteria codes

BP4			BP4_MODERATE Computational predictor scores (BayesDel =-0.2779; 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).
PM2_Supporting			This variant has an allele frequency of 0.000006780 (8/1180002 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).
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). This alteration behaved similar to wild type in DNA binding, oligomerization, expression, stability and transcriptional activity. PubMed:9766574  Stabilization and tetramer formation similar to wild type. PubMed:20978130 
BS2_Supporting			This variant has been observed in 2-3 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; SCV000277448.6).

Not Met criteria codes

BA1			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
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			aGVGD (zebrafish) = Class C0; BayesDel = -0.2779 (<0.16); no splicing effect
PP4			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
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			Other residues have not been evaluated or are higher Grantham
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
    		
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