

Variant: *NM_000546.6(TP53):c.1025G>C (p.Arg342Pro)*

Version: 1.0

CA337802 [↗](#)

215996 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 6596a2a8-f9bc-4bad-b9fb-403dfe19364d

Approved on: 2024/9/6

Published on: 2024/9/6

HGVS expressions

NM_000546.6(TP53):c.1025G>C (p.Arg342Pro)

NM_000546.6:c.1025G>C

NC_000017.11:g.7670684C>G

CM000679.2:g.7670684C>G

NC_000017.10:g.7574002C>G

CM000679.1:g.7574002C>G

NC_000017.9:g.7514727C>G

NG_017013.2:g.21867G>C

ENST00000503591.2:c.1025G>C

ENST00000508793.6:c.1025G>C

ENST00000509690.6:c.629G>C

ENST00000514944.6:c.746G>C

ENST00000604348.6:c.1004G>C

ENST00000269305.9:c.1025G>C

ENST00000269305.8:c.1025G>C

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

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

ENST00000420246.6:c.*132G>C

ENST00000445888.6:c.1025G>C

ENST00000455263.6:c.*44G>C

ENST00000504290.5:c.*44G>C

ENST00000504937.5:c.629G>C

ENST00000510385.5:c.*132G>C

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

ENST00000610292.4:c.908G>C

ENST00000610538.4:c.*44G>C

ENST00000610623.4:c.*44G>C

ENST00000615910.4:c.992G>C

ENST00000617185.4:c.*132G>C

ENST00000618944.4:c.*132G>C

ENST00000619186.4:c.548G>C

ENST00000619485.4:c.908G>C

ENST00000620739.4:c.908G>C

ENST00000622645.4:c.*132G>C

ENST00000635293.1:c.908G>C

NM_000546.5:c.1025G>C

NM_001126112.2:c.1025G>C

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

Pathogenic

Met criteria codes6

PP1_StrongPS3PM1_SupportingPS4_ModeratePP3PM2_Supporting

Not Met criteria codes12

PM5PM4BS2BS1BS4BS3PVS1PS1PS2BP4BA1PP4

Evidence Links0

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>C variant in TP53 is a missense variant predicted to cause substitution of arginine by proline at amino acid 342 (p.Arg342Pro). This variant has been reported in 3 unrelated families meeting Classic criteria. Based on this evidence, this variant scores 3 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMIDs 25981898, 25226867, 19714490). The variant has been reported to segregate with LFS-associated cancers in ≥ 7 meioses from 3 families (PP1_Strong; PMIDs 25981898, 25226867, 19714490). In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation, loss of growth suppression activity, and impaired tetramer formation indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 16007150). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Computational predictor scores (BayesDel = 0.24; Align GVGD = Class C35) 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 8 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspot by the Clingen TP53 VCEP (2-9 somatic occurrences, PMID: 30311369) (PM1_Supporting). In summary, this variant meets the criteria to be classified as Pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS4_Moderate, PP1_Strong, PS3, PM2_Supporting, PP3, PM1_Supporting. (Bayesian Points: 13; VCEP specifications version 2.0; 9/6/2024)

Met criteria codes

PP1_Strong			The variant has been reported to segregate with LFS-associated cancers in ≥ 7 meioses from 3 families (PP1_Strong; PMIDs 25981898, 25226867, 19714490).
PS3			In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation, loss of growth suppression activity, and impaired tetramer formation indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 16007150).
PM1_Supporting			This variant has 8 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspot by the Clingen TP53 VCEP (2-9 somatic occurrences, PMID: 30311369) (PM1_Supporting).
PS4_Moderate			This variant has been reported in 3 unrelated families meeting Classic criteria. Based on this evidence, this variant scores 3 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMIDs 25981898, 25226867, 19714490).
PP3			Computational predictor scores (BayesDel = 0.24; Align GVGD = Class C35) 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).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PM5			3 different missense variants (p.Arg342Leu, p.Arg342Gln, p.Arg342Gly) in the same codon have been reported (ClinVar Variation IDs: 1055894, 233136, 1769035). 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).
PM4			

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline			
BS2			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
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			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
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			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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