

Variant: *NM_000546.5(TP53):c.800G>A (p.Arg267Gln)*

Version: 3.0

CA000424 [↗](#)

127823 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: ca16e21b-853c-433e-88e5-601b2de6c525

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HGVS expressions

NM_000546.5(TP53):c.800G>A (p.Arg267Gln)

NM_000546.5:c.800G>A

NC_000017.11:g.7673820C>T

CM000679.2:g.7673820C>T

NC_000017.10:g.7577138C>T

CM000679.1:g.7577138C>T

NC_000017.9:g.7517863C>T

NG_017013.2:g.18731G>A

ENST00000503591.2:c.800G>A

ENST00000508793.6:c.800G>A

ENST00000509690.6:c.404G>A

ENST00000514944.6:c.521G>A

ENST00000604348.6:c.779G>A

ENST00000269305.9:c.800G>A

ENST00000269305.8:c.800G>A

ENST00000359597.8:c.800G>A

ENST00000413465.6:c.782+361G>A

ENST00000420246.6:c.800G>A

ENST00000445888.6:c.800G>A

ENST00000455263.6:c.800G>A

ENST00000504290.5:c.404G>A

ENST00000504937.5:c.404G>A

ENST00000509690.5:c.404G>A

ENST00000510385.5:c.404G>A

ENST00000610292.4:c.683G>A

ENST00000610538.4:c.683G>A

ENST00000610623.4:c.323G>A

ENST00000615910.4:c.767G>A

ENST00000617185.4:c.800G>A

ENST00000618944.4:c.323G>A

ENST00000619186.4:c.323G>A

ENST00000619485.4:c.683G>A

ENST00000620739.4:c.683G>A

ENST00000622645.4:c.683G>A

ENST00000635293.1:c.683G>A

NM_001126112.2:c.800G>A

NM_001126113.2:c.800G>A

	NM_001126114.2:c.800G>A
	NM_001126115.1:c.404G>A
	NM_001126116.1:c.404G>A
	NM_001126117.1:c.404G>A
	NM_001126118.1:c.683G>A
	NM_001276695.1:c.683G>A
	NM_001276696.1:c.683G>A
	NM_001276697.1:c.323G>A
	NM_001276698.1:c.323G>A
	NM_001276699.1:c.323G>A
	NM_001276760.1:c.683G>A
	NM_001276761.1:c.683G>A
	NM_001276695.2:c.683G>A
	NM_001276696.2:c.683G>A
	NM_001276697.2:c.323G>A
	NM_001276698.2:c.323G>A
	NM_001276699.2:c.323G>A
	NM_001276760.2:c.683G>A
	NM_001276761.2:c.683G>A
	NM_000546.6:c.800G>A
	NM_001126112.3:c.800G>A
	NM_001126113.3:c.800G>A
	NM_001126114.3:c.800G>A
	NM_001126115.2:c.404G>A
	NM_001126116.2:c.404G>A
	NM_001126117.2:c.404G>A
	NM_001126118.2:c.683G>A
	NM_001276695.3:c.683G>A
	NM_001276696.3:c.683G>A
	NM_001276697.3:c.323G>A
	NM_001276698.3:c.323G>A
	NM_001276699.3:c.323G>A
	NM_001276760.3:c.683G>A
	NM_001276761.3:c.683G>A

Uncertain Significance

Met criteria codes7

BS2

PS2_Moderate

PM1_Supporting

PS4_Moderate

PP4_Moderate

PP3

PM2_Supporting

Not Met criteria codes11

PM5

BS1

BS4

BS3

PVS1

PS1

PS3

BP7

BP4

BA1

PP1

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 2.4.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.800G>A variant in TP53 is a missense variant predicted to cause substitution of Arginine by Glutamine at amino acid 267 (p.Arg267Gln). This variant has been identified as a de novo occurrence with confirmed parental relationships in one individual with a moderately LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; Internal contributor). This variant has been reported in 6 unrelated families meeting Revised Chompret 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; PMID: 25584008, Internal lab contributors). At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, Internal lab contributor). 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). This variant has an allele frequency of 0.000004959 (8/1613260 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has a subpopulation allele frequency of <0.00004 in all non-bottleneck populations with 2 or more alleles present (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and retained growth suppression activity suggesting that this variant does not impact protein function; however, all assays did not agree (BS3_Supporting not met; PMIDs: 12826609, 30224644, 29979965, 39774325).This variant has 4 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). Computational predictor scores (BayesDel = 0.5934; 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). Available evidence suggests that this variant may be an atypical low penetrance variant. At this time, the TP53 VCEP cannot curate variants for low-penetrance designation. In summary, this variant meets the criteria to be classified as variant of uncertain significance for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS2_Moderate, PP4_Moderate, PS4_Moderate, BS2, PP3, PM1_Supporting, PM2_Supporting. (Bayesian Points: 5; VCEP specifications version 2.4)

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).
PS2_Moderate			This variant has been identified as a de novo occurrence with confirmed parental relationships in one individual with a moderately LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; Internal contributor).
PM1_Supporting			This variant has 4 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 6 unrelated families meeting Revised Chompret criteria. Based on this evidence, this variant scores 3.5 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMID: 25584008, Internal lab contributors).
PP4_Moderate			At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, Internal lab contributor).
PP3			Computational predictor scores (BayesDel = 0.5934; 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 has an allele frequency of 0.000004959 (8/1613260 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has a subpopulation allele frequency of

<0.00004 in all non-bottleneck populations with 2 or more alleles present (PM2_Supporting).

Not Met criteria codes

PM5			4 different missense variants (c.800G>T, p.Arg267Leu; c.800G>C, p.Arg267Pro; c.799C>G, p.Arg267Gly; c.799C>T, p.Arg267Trp) in the same codon have been reported (ClinVar Variation IDs: 852206, 428867, 1761541, 141764). However, these variants do not meet criteria for PM5 code application (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 suggesting that this variant does not impact protein function; however, all assays did not agree (BS3_Supporting not met; PMIDs: 12826609, 30224644, 29979965, 39774325).
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
PS3			In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and retained growth suppression activity suggesting that this variant does not impact protein function; however, all assays did not agree (BS3_Supporting not met; PMIDs: 12826609, 30224644, 29979965, 39774325).
BP7			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
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

