

Variant: NM_001276761.2:c.892C>A

Version: 2.0

CA397832787 [↗](#)

1019612 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 94981547-1bc0-489e-8b9a-b5963be2d6de

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HGVS expressions

NM_001276761.2:c.892C>A

NC_000017.11:g.7670700G>T

CM000679.2:g.7670700G>T

NC_000017.10:g.7574018G>T

CM000679.1:g.7574018G>T

NC_000017.9:g.7514743G>T

NG_017013.2:g.21851C>A

ENST00000503591.2:c.1009C>A

ENST00000508793.6:c.1009C>A

ENST00000509690.6:c.613C>A

ENST00000514944.6:c.730C>A

ENST00000604348.6:c.988C>A

ENST00000269305.9:c.1009C>A

ENST00000269305.8:c.1009C>A

ENST00000359597.8:c.993+2835C>A

ENST00000413465.6:c.782+3481C>A

ENST00000420246.6:c.*116C>A

ENST00000445888.6:c.1009C>A

ENST00000455263.6:c.*28C>A

ENST00000504290.5:c.*28C>A

ENST00000504937.5:c.613C>A

ENST00000510385.5:c.*116C>A

ENST00000576024.1:c.54-1010C>A

ENST00000610292.4:c.892C>A

ENST00000610538.4:c.*28C>A

ENST00000610623.4:c.*28C>A

ENST00000615910.4:c.976C>A

ENST00000617185.4:c.*116C>A

ENST00000618944.4:c.*116C>A

ENST00000619186.4:c.532C>A

ENST00000619485.4:c.892C>A

ENST00000620739.4:c.892C>A

ENST00000622645.4:c.*116C>A

ENST00000635293.1:c.892C>A

NM_000546.5:c.1009C>A

NM_001126112.2:c.1009C>A

NM_001126113.2:c.*28C>A

NM_001126114.2:c.*116C>A
NM_001126115.1:c.613C>A
NM_001126116.1:c.*116C>A
NM_001126117.1:c.*28C>A
NM_001126118.1:c.892C>A
NM_001276695.1:c.*28C>A
NM_001276696.1:c.*116C>A
NM_001276697.1:c.532C>A
NM_001276698.1:c.*116C>A
NM_001276699.1:c.*28C>A
NM_001276760.1:c.892C>A
NM_001276761.1:c.892C>A
NM_001276695.2:c.*28C>A
NM_001276696.2:c.*116C>A
NM_001276697.2:c.532C>A
NM_001276698.2:c.*116C>A
NM_001276699.2:c.*28C>A
NM_001276760.2:c.892C>A
NM_000546.6:c.1009C>A
NM_001126112.3:c.1009C>A
NM_001126113.3:c.*28C>A
NM_001126114.3:c.*116C>A
NM_001126115.2:c.613C>A
NM_001126116.2:c.*116C>A
NM_001126117.2:c.*28C>A
NM_001126118.2:c.892C>A
NM_001276695.3:c.*28C>A
NM_001276696.3:c.*116C>A
NM_001276697.3:c.532C>A
NM_001276698.3:c.*116C>A
NM_001276699.3:c.*28C>A
NM_001276760.3:c.892C>A
NM_001276761.3:c.892C>A

Likely Pathogenic

Met criteria codes 6

- PM1_Supporting
- BP4
- PM2_Supporting
- PS4_Supporting
- PS3
- PM5_Supporting

Not Met criteria codes 10

- BS1
- BS4
- BS3
- BS2
- PS1
- PS2
- BA1
- PP1
- PP3
- PP4

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.1009C>A variant in TP53 is a missense variant predicted to cause substitution of arginine by serine at amino acid 337 (p.Arg337Ser). This variant has been reported in 2 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 1 total point meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMIDs, ClinVar SCVs, Internal lab contributors). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965). 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). Two missense variants (p.Arg337Pro, p.Arg337Leu) in the same codon have been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP’s specifications.(PM5_Supporting). Computational predictor scores (BayesDel = 0.154096; Align GVGD Class C35) are below the recommended thresholds (BayesDel < 0.16 and > -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). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS3, BP4, PM1_Supporting, PM2_Supporting, PM5_Supporting, PS4_Supporting. (Bayesian Points: 7; VCEP specifications version 2.3)

Met criteria codes

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).
BP4			Computational predictor scores (BayesDel = 0.154096; Align GVGD Class C35) are below the recommended thresholds (BayesDel < 0.16 and > -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).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS4_Supporting			This variant has been reported in 2 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 1 total point meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMIDs, ClinVar SCVs, Internal lab contributors).
PS3			In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965).
PM5_Supporting			Two missense variants (p.Arg337Pro, p.Arg337Leu) in the same codon have been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP’s specifications.(PM5_Supporting).

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

BS3			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
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
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

Curation History 	
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