

Variant: *NM_000546.6(TP53):c.656C>T (p.Pro219Leu)*

Version: 1.0

CA397839907 [↗](#)

826488 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 61d9fc98-9d3c-4239-88a3-9dfad2491b5e

Approved on: 2026/2/5

Published on: 2026/2/10

HGVS expressions

NM_000546.6(TP53):c.656C>T (p.Pro219Leu)

NM_000546.6:c.656C>T

NC_000017.11:g.7674875G>A

CM000679.2:g.7674875G>A

NC_000017.10:g.7578193G>A

CM000679.1:g.7578193G>A

NC_000017.9:g.7518918G>A

NG_017013.2:g.17676C>T

ENST00000503591.2:c.656C>T

ENST00000508793.6:c.656C>T

ENST00000509690.6:c.260C>T

ENST00000514944.6:c.377C>T

ENST00000604348.6:c.635C>T

ENST00000269305.9:c.656C>T

ENST00000269305.8:c.656C>T

ENST00000359597.8:c.656C>T

ENST00000413465.6:c.656C>T

ENST00000420246.6:c.656C>T

ENST00000445888.6:c.656C>T

ENST00000455263.6:c.656C>T

ENST00000504290.5:c.260C>T

ENST00000504937.5:c.260C>T

ENST00000505014.5:n.912C>T

ENST00000509690.5:c.260C>T

ENST00000510385.5:c.260C>T

ENST00000514944.5:c.377C>T

ENST00000574684.1:n.67+178C>T

ENST00000610292.4:c.539C>T

ENST00000610538.4:c.539C>T

ENST00000610623.4:c.179C>T

ENST00000615910.4:c.623C>T

ENST00000617185.4:c.656C>T

ENST00000618944.4:c.179C>T

ENST00000619186.4:c.179C>T

ENST00000619485.4:c.539C>T

ENST00000620739.4:c.539C>T

ENST00000622645.4:c.539C>T

ENST00000635293.1:c.539C>T
NM_000546.5:c.656C>T
NM_001126112.2:c.656C>T
NM_001126113.2:c.656C>T
NM_001126114.2:c.656C>T
NM_001126115.1:c.260C>T
NM_001126116.1:c.260C>T
NM_001126117.1:c.260C>T
NM_001126118.1:c.539C>T
NM_001276695.1:c.539C>T
NM_001276696.1:c.539C>T
NM_001276697.1:c.179C>T
NM_001276698.1:c.179C>T
NM_001276699.1:c.179C>T
NM_001276760.1:c.539C>T
NM_001276761.1:c.539C>T
NM_001276695.2:c.539C>T
NM_001276696.2:c.539C>T
NM_001276697.2:c.179C>T
NM_001276698.2:c.179C>T
NM_001276699.2:c.179C>T
NM_001276760.2:c.539C>T
NM_001276761.2:c.539C>T
NM_001126112.3:c.656C>T
NM_001126113.3:c.656C>T
NM_001126114.3:c.656C>T
NM_001126115.2:c.260C>T
NM_001126116.2:c.260C>T
NM_001126117.2:c.260C>T
NM_001126118.2:c.539C>T
NM_001276695.3:c.539C>T
NM_001276696.3:c.539C>T
NM_001276697.3:c.179C>T
NM_001276698.3:c.179C>T
NM_001276699.3:c.179C>T
NM_001276760.3:c.539C>T
NM_001276761.3:c.539C>T

Uncertain Significance

Met criteria codes 2

PM2_Supporting PP3_Moderate

Not Met criteria codes 14

BA1 BP4 BS1 BS4 BS3 BS2
PP1 PP4 PS1 PS2 PS3 PS4
PM1 PM5

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 2.4.0

Criteria Specification Approval History
Criteria Specifications for this VCEP

TP53 VCEP

The NM_000546.6: c.656C>T variant in TP53 is a missense variant predicted to cause substitution of proline by leucine at amino acid 219 (p.Pro219Leu). Although this variant has been observed in germline cases, to our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met; Internal lab contributors). This variant has an allele frequency of 6.195e-7 (1/1614106 alleles) across gnomAD v4.1.0 which is lower than the ClinGen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has no more than one allele per non-bottleneck subpopulation (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed conflicting results with respect to transactivation, growth suppression activity, and/or tetramer formation (PS3/BS3 not met; PMIDs: 12826609, 39774325, 29979965, 30224644). Computational predictor scores (BayesDel = 0.585695; Align GVGD = Class C65) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate). 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: PM2_Supporting, PP3_Moderate. (Bayesian Points: 3; VCEP specifications version 2.4)

Met criteria codes

PM2_Supporting			This variant has an allele frequency of 6.195e-7 (1/1614106 alleles) across gnomAD v4.1.0 which is lower than the ClinGen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has no more than one allele per non-bottleneck subpopulation (PM2_Supporting).
PP3_Moderate			Computational predictor scores (BayesDel = 0.585695; Align GVGD = Class C65) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate).

Not Met criteria codes

BA1			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
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 conflicting results with respect to transactivation, growth suppression activity, and/or tetramer formation (PS3/BS3 not met; PMIDs: 12826609, 39774325, 29979965, 30224644)
BS2			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

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			In vitro assays performed in yeast and/or human cell lines showed conflicting results with respect to transactivation, growth suppression activity, and/or tetramer formation (PS3/BS3 not met; PMIDs: 12826609, 39774325, 29979965, 30224644)
PS4			Although this variant has been observed in germline cases, to our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met; Internal lab contributors).
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			3 different missense variants (p.Pro219Ala, p.Pro219Thr, p.Pro219Ser) in the same codon have been reported (ClinVar Variation IDs: 2850523, 2758381, 245673). 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). P219L = 98 P219A = 27 (VUS ClinVar) P219T = 38 (VUS in ClinVar) P219S = 38 (VUS in ClinVar) P219R = 103 (VUS ClinVar)

Curation History [↗](#)



 

 

Showing 1 to 1 of 1 rows

--

