# *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**: 2026-02-05
**Published on**: 2026-02-10

## *HGVS expressions*

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

PM1 PM5 BA1 BS2 BS1 BS4 BS3 BP4 PS1 PS2 PS3 PS4 PP1 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 2.4.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***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 signficance 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**

| | | |
|---|---|---|
| **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) |
| **BA1** | ✖ | 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** | | ✖ | 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) |
| **BP4** | | ✖ | 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). |
| **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 |

## Curation History

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