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# *Variant: NM_000546.6(TP53):c.379T>C (p.Ser127Pro)*

Version: 1.0

*CA397843917*

*934410 (ClinVar)*

**Gene**: TP53 (HGNC:7157)
**Condition**: Li-Fraumeni syndrome (MONDO:0018875)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** 130cd553-8ab6-4a2a-8452-d95fd366c6e5
**Approved on**: 2026/3/4
**Published on**: 2026/4/22

## *HGVS expressions*

**NM_000546.6(TP53):c.379T>C (p.Ser127Pro)**
**NM_000546.6:c.379T>C**
NC_000017.11:g.7675233A>G
CM000679.2:g.7675233A>G
NC_000017.10:g.7578551A>G
CM000679.1:g.7578551A>G
NC_000017.9:g.7519276A>G
NG_017013.2:g.17318T>C
ENST00000503591.2:c.379T>C
ENST00000508793.6:c.379T>C
ENST00000509690.6:c.-18T>C
ENST00000514944.6:c.100T>C
ENST00000604348.6:c.376-18T>C
ENST00000269305.9:c.379T>C
ENST00000269305.8:c.379T>C
ENST00000359597.8:c.379T>C
ENST00000413465.6:c.379T>C
ENST00000420246.6:c.379T>C
ENST00000445888.6:c.379T>C
ENST00000455263.6:c.379T>C
ENST00000503591.1:c.379T>C
ENST00000504290.5:c.-18T>C
ENST00000504937.5:c.-18T>C
ENST00000505014.5:n.635T>C
ENST00000508793.5:c.379T>C
ENST00000509690.5:c.-18T>C
ENST00000510385.5:c.-18T>C
ENST00000514944.5:c.100T>C
ENST00000604348.5:c.376-18T>C
ENST00000610292.4:c.262T>C
ENST00000610538.4:c.262T>C
ENST00000610623.4:c.-99T>C
ENST00000615910.4:c.346T>C
ENST00000617185.4:c.379T>C
ENST00000618944.4:c.-99T>C
ENST00000619186.4:c.-99T>C
ENST00000619485.4:c.262T>C

ENST00000620739.4:c.262T>C
ENST00000622645.4:c.262T>C
ENST00000635293.1:c.262T>C
NM_000546.5:c.379T>C
NM_001126112.2:c.379T>C
NM_001126113.2:c.379T>C
NM_001126114.2:c.379T>C
NM_001126115.1:c.-18T>C
NM_001126116.1:c.-18T>C
NM_001126117.1:c.-18T>C
NM_001126118.1:c.262T>C
NM_001276695.1:c.262T>C
NM_001276696.1:c.262T>C
NM_001276697.1:c.-99T>C
NM_001276698.1:c.-99T>C
NM_001276699.1:c.-99T>C
NM_001276760.1:c.262T>C
NM_001276761.1:c.262T>C
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NM_001276696.2:c.262T>C
NM_001276697.2:c.-99T>C
NM_001276698.2:c.-99T>C
NM_001276699.2:c.-99T>C
NM_001276760.2:c.262T>C
NM_001276761.2:c.262T>C
NM_001126112.3:c.379T>C
NM_001126113.3:c.379T>C
NM_001126114.3:c.379T>C
NM_001126115.2:c.-18T>C
NM_001126116.2:c.-18T>C
NM_001126117.2:c.-18T>C
NM_001126118.2:c.262T>C
NM_001276695.3:c.262T>C
NM_001276696.3:c.262T>C
NM_001276697.3:c.-99T>C
NM_001276698.3:c.-99T>C
NM_001276699.3:c.-99T>C
NM_001276760.3:c.262T>C
NM_001276761.3:c.262T>C

**Likely Pathogenic**

**Met criteria codes** 5

PM1_Supporting PP3_Moderate PS3 PP4 PM2_Supporting

**Not Met criteria codes** 11

PM5 BA1 BS2 BS1 BS4 BS3 BP4 PS1 PS2 PS4 PP1

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(TP53):c.379T>C variant in TP53 is a missense variant predicted to cause substitution of serine by proline at amino acid 127 (p.Ser127Pro). 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). At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, Internal lab contributor). 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 by the majority of available assays indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965, 39774325). Computational predictor scores (BayesDel = 0.58628; 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). 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). 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: PP4, PS3, PP3_moderate, PM1_supporting, PM2_supporting. (Bayesian Points: 9; VCEP specifications version 2.4)**

**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). |
| **PP3_Moderate** | ✔ | Computational predictor scores (BayesDel = 0.58628; 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). |
| **PS3** | ✔ | In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity by the majority of available assays indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965, 39774325). |
| **PP4** | ✔ | At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, Internal lab contributor). |
| **PM2_Supporting** | ✔ | This variant is absent from gnomAD v4.1.0 (PM2_Supporting). |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PM5** | ✖ | Another missense variant (p.Ser127Thr) (ClinVar Variation ID: 824232), with Grantham score equal to or less than the current variant in the same codon has been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications. However, this variant does not meet criteria for PM5 code application as it does not have clinical data that counts towards pathogenicity (PM5 not met). |
| **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** | | ✖ | 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 |
| **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 |
| **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 |

## Curation History

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