

Variant: NM_000546.5(TP53):c.455C>T (p.Pro152Leu)

Version: 1.1

CA000204 [↗](#)

142766 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 6bf64717-7983-4329-bddb-4b28f0690106

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HGVS expressions

NM_000546.5(TP53):c.455C>T (p.Pro152Leu)

NM_000546.5:c.455C>T

NC_000017.11:g.7675157G>A

CM000679.2:g.7675157G>A

NC_000017.10:g.7578475G>A

CM000679.1:g.7578475G>A

NC_000017.9:g.7519200G>A

NG_017013.2:g.17394C>T

ENST00000503591.2:c.455C>T

ENST00000508793.6:c.455C>T

ENST00000509690.6:c.59C>T

ENST00000514944.6:c.176C>T

ENST00000604348.6:c.434C>T

ENST00000269305.9:c.455C>T

ENST00000269305.8:c.455C>T

ENST00000359597.8:c.455C>T

ENST00000413465.6:c.455C>T

ENST00000420246.6:c.455C>T

ENST00000445888.6:c.455C>T

ENST00000455263.6:c.455C>T

ENST00000504290.5:c.59C>T

ENST00000504937.5:c.59C>T

ENST00000505014.5:n.711C>T

ENST00000508793.5:c.455C>T

ENST00000509690.5:c.59C>T

ENST00000510385.5:c.59C>T

ENST00000514944.5:c.176C>T

ENST00000610292.4:c.338C>T

ENST00000610538.4:c.338C>T

ENST00000610623.4:c.-23C>T

ENST00000615910.4:c.422C>T

ENST00000617185.4:c.455C>T

ENST00000618944.4:c.-23C>T

ENST00000619186.4:c.-23C>T

ENST00000619485.4:c.338C>T

ENST00000620739.4:c.338C>T

ENST00000622645.4:c.338C>T

	ENST00000635293.1:c.338C>T
	NM_001126112.2:c.455C>T
	NM_001126113.2:c.455C>T
	NM_001126114.2:c.455C>T
	NM_001126115.1:c.59C>T
	NM_001126116.1:c.59C>T
	NM_001126117.1:c.59C>T
	NM_001126118.1:c.338C>T
	NM_001276695.1:c.338C>T
	NM_001276696.1:c.338C>T
	NM_001276697.1:c.-23C>T
	NM_001276698.1:c.-23C>T
	NM_001276699.1:c.-23C>T
	NM_001276760.1:c.338C>T
	NM_001276761.1:c.338C>T
	NM_001276695.2:c.338C>T
	NM_001276696.2:c.338C>T
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	NM_001276698.2:c.-23C>T
	NM_001276699.2:c.-23C>T
	NM_001276760.2:c.338C>T
	NM_001276761.2:c.338C>T
	NM_000546.6:c.455C>T
	NM_001126112.3:c.455C>T
	NM_001126113.3:c.455C>T
	NM_001126114.3:c.455C>T
	NM_001126115.2:c.59C>T
	NM_001126116.2:c.59C>T
	NM_001126117.2:c.59C>T
	NM_001126118.2:c.338C>T
	NM_001276695.3:c.338C>T
	NM_001276696.3:c.338C>T
	NM_001276697.3:c.-23C>T
	NM_001276698.3:c.-23C>T
	NM_001276699.3:c.-23C>T
	NM_001276760.3:c.338C>T
	NM_001276761.3:c.338C>T

Pathogenic

Met criteria codes 7

- PP4_Moderate
- PS3
- PS4
- PP1
- PM2_Supporting
- PM1
- PP3_Moderate

Not Met criteria codes 10

- BA1
- BS2
- BS1
- BS4
- BS3
- PVS1
- BP4
- PS1
- PS2
- 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 2.0.0

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)

TP53 VCEP

The NM_000546.6: c.455C>T variant in TP53 is a missense variant predicted to cause substitution of proline by leucine at amino acid 152 (p.Pro152Leu). This variant has been reported in 14 unrelated probands/families meeting Classic or Revised Chompret criteria, and reported in 1 individual under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 8.5 total points meeting the TP53 VCEP phenotype scoring criteria of ≥ 8 points. (PS4_Very Strong; PMIDs26014290, 15654278, 10486318, 25584008, 17308077, Internal lab contributors; SCV000218779.10, SCV000187230.8). The variant has been reported to segregate with LFS-associated cancers in 4 meioses in 2 families (PP1; PMID: 10486318, Internal lab contributors SCV000187230.8). 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 contributors SCV000187230.8). This variant has an allele frequency of 0.000001695 (2/1180036 alleles) in the European (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (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 28 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 (PM1, ≥ 10 somatic occurrences, PMID: 30311369). Computational predictor scores (BayesDel =0.558; 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 Pathogenic for Li Fraumeni Syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS4_Very Strong, PP4_Moderate, PP1, PM2_Supporting, PS3, PM1, PP3_Moderate. (Bayesian Points: 20; VCEP specifications version 2.0; 7/24/2024).

Met criteria codes

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 contributors SCV000187230.8).
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).
PS4			PS4_VERY STRONG This variant has been reported in 14 unrelated probands/families meeting Classic or Revised Chompret criteria, and reported in 1 individual under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 8.5 total points meeting the TP53 VCEP phenotype scoring criteria of ≥ 8 points. (PS4_Very Strong; PMIDs26014290, 15654278, 10486318, 25584008, 17308077, Internal lab contributors; SCV000218779.10, SCV000187230.8).
PP1			The variant has been reported to segregate with LFS-associated cancers in 4 meioses in 2 families (PP1; PMID: 10486318, Internal lab contributors SCV000187230.8).
PM2_Supporting			This variant has an allele frequency of 0.000001695 (2/1180036 alleles) in the European (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
PM1			This variant has 28 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 (≥ 10 somatic occurrences, PMID: 30311369).

PP3_Moderate			Computational predictor scores (BayesDel =0.558; Align GVG D = Class C65) are above recommended thresholds (BayesDel > 0.16 and an Align GVG D 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
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
PVS1			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
PM5			3 different missense variants (c.455C>A p.Pro152Gln, c.455C>G p.Pro152Arg, c.454C>T p.Pro152Ser) in the same codon have been reported (ClinVar Variation IDs 1058730, 824998, 482230). 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).



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