

Variant: *NM_000546.6(TP53):c.659A>G (p.Tyr220Cys)*

Version: 1.1

CA000315 [↗](#)

127819 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 4795612b-c5d2-4229-a5ec-172fedfbcf55

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HGVS expressions

NM_000546.6:c.659A>G

NM_000546.6(TP53):c.659A>G (p.Tyr220Cys)

NC_000017.11:g.7674872T>C

CM000679.2:g.7674872T>C

NC_000017.10:g.7578190T>C

CM000679.1:g.7578190T>C

NC_000017.9:g.7518915T>C

NG_017013.2:g.17679A>G

ENST00000503591.2:c.659A>G

ENST00000508793.6:c.659A>G

ENST00000509690.6:c.263A>G

ENST00000514944.6:c.380A>G

ENST00000604348.6:c.638A>G

ENST00000269305.9:c.659A>G

ENST00000269305.8:c.659A>G

ENST00000359597.8:c.659A>G

ENST00000413465.6:c.659A>G

ENST00000420246.6:c.659A>G

ENST00000445888.6:c.659A>G

ENST00000455263.6:c.659A>G

ENST00000504290.5:c.263A>G

ENST00000504937.5:c.263A>G

ENST00000505014.5:n.915A>G

ENST00000509690.5:c.263A>G

ENST00000510385.5:c.263A>G

ENST00000514944.5:c.380A>G

ENST00000574684.1:n.67+181A>G

ENST00000610292.4:c.542A>G

ENST00000610538.4:c.542A>G

ENST00000610623.4:c.182A>G

ENST00000615910.4:c.626A>G

ENST00000617185.4:c.659A>G

ENST00000618944.4:c.182A>G

ENST00000619186.4:c.182A>G

ENST00000619485.4:c.542A>G

ENST00000620739.4:c.542A>G

ENST00000622645.4:c.542A>G

ENST00000635293.1:c.542A>G

NM_000546.5:c.659A>G

NM_001126112.2:c.659A>G

NM_001126113.2:c.659A>G

NM_001126114.2:c.659A>G

NM_001126115.1:c.263A>G

NM_001126116.1:c.263A>G

NM_001126117.1:c.263A>G

NM_001126118.1:c.542A>G

NM_001276695.1:c.542A>G

NM_001276696.1:c.542A>G

NM_001276697.1:c.182A>G

NM_001276698.1:c.182A>G

NM_001276699.1:c.182A>G

NM_001276760.1:c.542A>G

NM_001276761.1:c.542A>G

NM_001276695.2:c.542A>G

NM_001276696.2:c.542A>G

NM_001276697.2:c.182A>G

NM_001276698.2:c.182A>G

NM_001276699.2:c.182A>G

NM_001276760.2:c.542A>G

NM_001276761.2:c.542A>G

NM_001126112.3:c.659A>G

NM_001126113.3:c.659A>G

NM_001126114.3:c.659A>G

NM_001126115.2:c.263A>G

NM_001126116.2:c.263A>G

NM_001126117.2:c.263A>G

NM_001126118.2:c.542A>G

NM_001276695.3:c.542A>G

NM_001276696.3:c.542A>G

NM_001276697.3:c.182A>G

NM_001276698.3:c.182A>G

NM_001276699.3:c.182A>G

NM_001276760.3:c.542A>G

NM_001276761.3:c.542A>G

Pathogenic

Met criteria codes **8**

PM2_Supporting PS2_Moderate
PP4_Moderate PS3 PS4 PM1
PP3_Moderate PP1_Strong

Not Met criteria codes **10**

BA1 BS1 BS3 BS2 BP7 BP4
PS1 PM5 PM6 PVS1

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.659A>G variant in TP53 is a missense variant predicted to cause substitution of Tyrosine by Cysteine at amino acid 220 (p.Tyr220Cys). This variant has been reported in 9 unrelated probands and/or families meeting Classic and/or Revised Chompret criteria. Based on this evidence, this variant scores 6.5 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMIDs: 20028212, 9242456, 19101993, 18307025, 20805372, 21761402, 27714481, 10589545, 10432928, 8118819, ClinVar SCV: SCV000183774.8, Internal lab contributors). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with an LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; PMID: 18307025). The variant has been reported to segregate with LFS-associated cancers in ≥ 7 meioses from 5 families (PP1_Strong; PMIDs: 20028212, 1910993, 10432928, 8118819, 27714481). 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, ClinVar GTRs, SCV000183774.8). This variant has an allele frequency of 0.000005932 (7/1179948 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 (PMIDs: 12826609, 30224644, 29979965) (PS3). This variant has 127 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) (PM1). Computational predictor scores (BayesDel = 0.5625; 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, PS2_Moderate, PP1_Strong, PM2_Supporting, PS3, PM1, PP3_Moderate, PP4_Moderate (Bayesian Points: 21 points; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

PM2_Supporting	 	This variant has an allele frequency of 0.000005932 (7/1179948 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).
PS2_Moderate	 	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with an LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; PMID: 18307025).
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, ClinVar GTRs, SCV000183774.8).
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 (PMIDs: 12826609, 30224644, 29979965) (PS3).
PS4	 	This variant has been reported in 9 unrelated probands and/or families meeting Classic and/or Revised Chompret criteria. Based on this evidence, this variant scores 6.5 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMIDs: 20028212, 9242456, 19101993, 18307025, 20805372, 21761402, 27714481, 10589545, 10432928, 8118819, ClinVar SCV: SCV000183774.8, Internal lab contributors).
PM1	 	This variant has 127 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) (PM1).

PP3_Moderate			Computational predictor scores (BayesDel = 0.5625; 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).
PP1_Strong			The variant has been reported to segregate with LFS-associated cancers in ≥ 7 meioses from 5 families (PP1_Strong; PMIDs: 20028212, 1910993, 10432928, 8118819, 27714481).

Not Met criteria codes

BA1			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
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
BP7			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
PM5			4 different missense variants (c.659A>C, p.Try220Ser; c.658T>G, p.Tyr220Asp; c.658T>A, p.Tyr220Asn, c.658T>C, p.Tyr220His) in the same codon have been reported (ClinVar Variation IDs: 12383, 376689, 376688, 376687). 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).
PM6			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

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