

Variant: NM_001126115.1(TP53):c.182A>C (p.His61Pro)

Version: 1.1

CA16603033 [↗](#)

376612 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: b7079914-1dfb-4bb9-8f67-f466a0532ac1

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HGVS expressions

NM_001126115.1:c.182A>C

NM_001126115.1(TP53):c.182A>C (p.His61Pro)

NC_000017.11:g.7674953T>G

CM000679.2:g.7674953T>G

NC_000017.10:g.7578271T>G

CM000679.1:g.7578271T>G

NC_000017.9:g.7518996T>G

NG_017013.2:g.17598A>C

ENST00000503591.2:c.578A>C

ENST00000508793.6:c.578A>C

ENST00000509690.6:c.182A>C

ENST00000514944.6:c.299A>C

ENST00000604348.6:c.557A>C

ENST00000269305.9:c.578A>C

ENST00000269305.8:c.578A>C

ENST00000359597.8:c.578A>C

ENST00000413465.6:c.578A>C

ENST00000420246.6:c.578A>C

ENST00000445888.6:c.578A>C

ENST00000455263.6:c.578A>C

ENST00000504290.5:c.182A>C

ENST00000504937.5:c.182A>C

ENST00000505014.5:n.834A>C

ENST00000509690.5:c.182A>C

ENST00000510385.5:c.182A>C

ENST00000514944.5:c.299A>C

ENST00000574684.1:n.67+100A>C

ENST00000610292.4:c.461A>C

ENST00000610538.4:c.461A>C

ENST00000610623.4:c.101A>C

ENST00000615910.4:c.545A>C

ENST00000617185.4:c.578A>C

ENST00000618944.4:c.101A>C

ENST00000619186.4:c.101A>C

ENST00000619485.4:c.461A>C

ENST00000620739.4:c.461A>C

ENST00000622645.4:c.461A>C

ENST00000635293.1:c.461A>C
NM_000546.5:c.578A>C
NM_001126112.2:c.578A>C
NM_001126113.2:c.578A>C
NM_001126114.2:c.578A>C
NM_001126116.1:c.182A>C
NM_001126117.1:c.182A>C
NM_001126118.1:c.461A>C
NM_001276695.1:c.461A>C
NM_001276696.1:c.461A>C
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NM_001276698.1:c.101A>C
NM_001276699.1:c.101A>C
NM_001276760.1:c.461A>C
NM_001276761.1:c.461A>C
NM_001276695.2:c.461A>C
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NM_001276760.2:c.461A>C
NM_001276761.2:c.461A>C
NM_000546.6:c.578A>C
NM_001126112.3:c.578A>C
NM_001126113.3:c.578A>C
NM_001126114.3:c.578A>C
NM_001126115.2:c.182A>C
NM_001126116.2:c.182A>C
NM_001126117.2:c.182A>C
NM_001126118.2:c.461A>C
NM_001276695.3:c.461A>C
NM_001276696.3:c.461A>C
NM_001276697.3:c.101A>C
NM_001276698.3:c.101A>C
NM_001276699.3:c.101A>C
NM_001276760.3:c.461A>C
NM_001276761.3:c.461A>C

Pathogenic

Met criteria codes 6

PM2_Supporting PM1_Supporting
PP4 PS2 PS3 PP3_Moderate

Not Met criteria codes 12

BA1 BP7 BP4 BS1 BS4 BS3
BS2 PP1 PS1 PS4 PM5
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.578A>C variant in TP53 is a missense variant predicted to cause substitution of histidine by proline at amino acid 193 (p.His193Pro). In vitro assays performed in yeast and 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). Computational predictor scores (BayesDel = 0.5922; 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 been identified as a de novo occurrence with confirmed parental relationships in 1 individual with a strongly-associated LFS-associated cancer totaling 4 phenotype points (PS2; PMID: 19556618). At least one individual with this variant was found to have a variant allele fraction of 25-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, Internal lab contributor: SCV002651939.1). This variant has an allele frequency of 6.196e-7 (1/1614048 alleles) across gnomAD v4.1.0 which is lower than the ClinGen TP53 VCEP threshold (<0.00003) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). This variant has 8 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 Pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS3, PP3_Moderate, PS2, PP4, PM2_Supporting, PM1_Supporting. (Bayesian Points: 13; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

PM2_Supporting			This variant has an allele frequency of 6.196e-7 (1/1614048 alleles) across gnomAD v4.1.0 which is lower than the ClinGen TP53 VCEP threshold (<0.00003) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
PM1_Supporting			This variant has 8 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).
PP4			At least one individual with this variant was found to have a variant allele fraction of 25-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, Internal lab contributor: SCV002651939.1).
PS2			This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with a strongly-associated LFS-associated cancer totaling 4 phenotype points (PS2; PMID: 19556618).
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).
PP3_Moderate			Computational predictor scores (BayesDel = 0.5922; 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
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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
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
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
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			This variant received a total of 0.5 points across 1 unrelated family. (PS4 not met; PMID: 28369373).
PM5			6 different missense variants (p.His193Gln; p.His193Leu; p.His193Arg; p.His193Asn; p.His193Asp; p.His193Tyr) in the same codon have been reported (ClinVar Variation IDs: 825975, 185822, 184979, 376614, 376613, 230256). 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).
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 

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