The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
Approved on: 2024/8/5
Published on: 2024/8/5

HGVS expressions

NM_001126115.1(TP53):c.182A>C (p.His61Pro)
NM_001126115.1:c.182A>C
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
NM_001276697.1:c.101A>C
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_001276699.2:c.101A>C
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
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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

PM1_Supporting PP3_Moderate PS2 PS3 PP4 PM2_Supporting

Not Met criteria codes 12

PVS1 PM5 BA1 BS2 BS1 BS4 BS3 BP7 BP4 PS1 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 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

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

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).
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).
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).
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).
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).

Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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).
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
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
PS4		✖	This variant received a total of 0.5 points across 1 unrelated family. (PS4 not met; PMID: 28369373).
PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 2 of 2 rows

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