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_000546.6(TP53):c.472C>T (p.Arg158Cys)

Version: 1.0

CA000225

127812 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: e0f57545-5b3c-476f-bb86-150cbdaedf7a
Approved on: 2025/12/4
Published on: 2026/1/14

HGVS expressions

NM_000546.6(TP53):c.472C>T (p.Arg158Cys)
NM_000546.6:c.472C>T
NC_000017.11:g.7675140G>A
CM000679.2:g.7675140G>A
NC_000017.10:g.7578458G>A
CM000679.1:g.7578458G>A
NC_000017.9:g.7519183G>A
NG_017013.2:g.17411C>T
ENST00000503591.2:c.472C>T
ENST00000508793.6:c.472C>T
ENST00000509690.6:c.76C>T
ENST00000514944.6:c.193C>T
ENST00000604348.6:c.451C>T
ENST00000269305.9:c.472C>T
ENST00000269305.8:c.472C>T
ENST00000359597.8:c.472C>T
ENST00000413465.6:c.472C>T
ENST00000420246.6:c.472C>T
ENST00000445888.6:c.472C>T
ENST00000455263.6:c.472C>T
ENST00000504290.5:c.76C>T
ENST00000504937.5:c.76C>T
ENST00000505014.5:n.728C>T
ENST00000508793.5:c.472C>T
ENST00000509690.5:c.76C>T
ENST00000510385.5:c.76C>T
ENST00000514944.5:c.193C>T
ENST00000610292.4:c.355C>T
ENST00000610538.4:c.355C>T
ENST00000610623.4:c.-6C>T
ENST00000615910.4:c.439C>T
ENST00000617185.4:c.472C>T
ENST00000618944.4:c.-6C>T
ENST00000619186.4:c.-6C>T
ENST00000619485.4:c.355C>T
ENST00000620739.4:c.355C>T
ENST00000622645.4:c.355C>T

ENST00000635293.1:c.355C>T
NM_000546.5:c.472C>T
NM_001126112.2:c.472C>T
NM_001126113.2:c.472C>T
NM_001126114.2:c.472C>T
NM_001126115.1:c.76C>T
NM_001126116.1:c.76C>T
NM_001126117.1:c.76C>T
NM_001126118.1:c.355C>T
NM_001276695.1:c.355C>T
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NM_001276697.1:c.-6C>T
NM_001276698.1:c.-6C>T
NM_001276699.1:c.-6C>T
NM_001276760.1:c.355C>T
NM_001276761.1:c.355C>T
NM_001276695.2:c.355C>T
NM_001276696.2:c.355C>T
NM_001276697.2:c.-6C>T
NM_001276698.2:c.-6C>T
NM_001276699.2:c.-6C>T
NM_001276760.2:c.355C>T
NM_001276761.2:c.355C>T
NM_001126112.3:c.472C>T
NM_001126113.3:c.472C>T
NM_001126114.3:c.472C>T
NM_001126115.2:c.76C>T
NM_001126116.2:c.76C>T
NM_001126117.2:c.76C>T
NM_001126118.2:c.355C>T
NM_001276695.3:c.355C>T
NM_001276696.3:c.355C>T
NM_001276697.3:c.-6C>T
NM_001276698.3:c.-6C>T
NM_001276699.3:c.-6C>T
NM_001276760.3:c.355C>T
NM_001276761.3:c.355C>T

Uncertain Significance

Met criteria codes 3

PM2_Supporting BS2_Supporting PP3_Moderate

Not Met criteria codes 15

PP1 PP4 BA1 PM6 PVS1 PM1 PM5 BS1 BS4 BS3 PS1 PS2 PS3 PS4 BP4

Evidence Links 4

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: c.472C>T variant in TP53 is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 158 (p.Arg158Cys). This variant has been observed in 2-3 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Supporting; Internal lab contributor). This variant received a total of 0.5 points across 1 probands. However, PS4 cannot be applied because there there are not enough cases to reach the 1 point minimum to apply PS4_Supporting (PS4 not met; PMID 22170717). In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and retained growth suppression activity suggesting that this variant does not impact protein function; however, all assays did not agree (BS3_Supporting not met; PMIDs: 12826609, 30224644, 29979965, 39774325). This variant has an allele frequency of 0.000004337 (7/1614070 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has a subpopulation allele frequency of <0.00004 in all non-bottleneck populations with 2 or more alleles present (PM2_Supporting). Computational predictor scores (BayesDel = 0.51; Align GVGD = Class 65) 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 variant of uncertain significance for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PP3_Moderate, BS2_Supporting, PM2_Supporting. (Bayesian Points: 2; VCEP specifications version 2.4)

Met criteria codes

PM2_Supporting	✔	This variant has an allele frequency of 0.000004337 (7/1614070 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has a subpopulation allele frequency of <0.00004 in all non-bottleneck populations with 2 or more alleles present (PM2_Supporting).
BS2_Supporting	✔	This variant has been observed in 2-3 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Supporting; Internal lab contributor).
PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.51; Align GVGD = Class 65) 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

PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
PM1	✖	This variant does not reside within a region of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PM1 not met).
PM5	✖	2 different missense variants(p.Arg158Leu, p.Arg158Pro) in the same codon have been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications. However, this variant does not have any applicable functional data while other residues have pathogenic functional data (PM5 Not Met).
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	✖	In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and retained growth suppression activity suggesting that this variant does not impact protein function; however, all assays did not agree (BS3_Supporting not met; PMIDs: 12826609, 30224644, 29979965, 39774325). LOF **PubMed:39774325** No LOF **PubMed:29979965** Partially functional **PubMed:12826609** No LOF **PubMed:30224644**
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
PS3	✖	In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and retained growth suppression activity suggesting that this variant does not impact protein function; however, all assays did not agree (BS3_Supporting not met; PMIDs: 12826609, 30224644, 29979965, 39774325). LOF **PubMed:39774325** No LOF **PubMed:29979965** Partially functional **PubMed:12826609** No LOF **PubMed:30224644**
PS4	✖	This variant received a total of 0.5 points across 1 probands. However, PS4 cannot be applied because there there are not enough cases to reach the 1 point minimum to apply PS4_Supporting (PS4 not met; PMID 22170717).
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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