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.188C>G (p.Ala63Gly)

Version: 2.0

CA10580957

229693 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: e2b86e34-c2dd-4cfe-97f2-92af3ac253cc
Approved on: 2025/1/16
Published on: 2025/1/16

HGVS expressions

NM_000546.6(TP53):c.188C>G (p.Ala63Gly)
NM_000546.6:c.188C>G
NC_000017.11:g.7676181G>C
CM000679.2:g.7676181G>C
NC_000017.10:g.7579499G>C
CM000679.1:g.7579499G>C
NC_000017.9:g.7520224G>C
NG_017013.2:g.16370C>G
ENST00000503591.2:c.188C>G
ENST00000508793.6:c.188C>G
ENST00000509690.6:c.-21-945C>G
ENST00000514944.6:c.96+201C>G
ENST00000604348.6:c.188C>G
ENST00000269305.9:c.188C>G
ENST00000269305.8:c.188C>G
ENST00000359597.8:c.188C>G
ENST00000413465.6:c.188C>G
ENST00000420246.6:c.188C>G
ENST00000445888.6:c.188C>G
ENST00000455263.6:c.188C>G
ENST00000503591.1:c.188C>G
ENST00000505014.5:n.444C>G
ENST00000508793.5:c.188C>G
ENST00000509690.5:c.-21-945C>G
ENST00000514944.5:c.96+201C>G
ENST00000604348.5:c.188C>G
ENST00000610292.4:c.71C>G
ENST00000610538.4:c.71C>G
ENST00000615910.4:c.188C>G
ENST00000617185.4:c.188C>G
ENST00000619485.4:c.71C>G
ENST00000620739.4:c.71C>G
ENST00000622645.4:c.71C>G
ENST00000635293.1:c.71C>G
NM_000546.5:c.188C>G
NM_001126112.2:c.188C>G
NM_001126113.2:c.188C>G

NM_001126114.2:c.188C>G
NM_001126118.1:c.71C>G
NM_001276695.1:c.71C>G
NM_001276696.1:c.71C>G
NM_001276760.1:c.71C>G
NM_001276761.1:c.71C>G
NM_001276695.2:c.71C>G
NM_001276696.2:c.71C>G
NM_001276760.2:c.71C>G
NM_001276761.2:c.71C>G
NM_001126112.3:c.188C>G
NM_001126113.3:c.188C>G
NM_001126114.3:c.188C>G
NM_001126118.2:c.71C>G
NM_001276695.3:c.71C>G
NM_001276696.3:c.71C>G
NM_001276760.3:c.71C>G
NM_001276761.3:c.71C>G

Likely Benign

Met criteria codes 4

BS3 PM2_Supporting BP4 BS2_Supporting

Not Met criteria codes 13

BS1 BS4 PM1 PM5 PM6 PS1 PS2 PS3 PS4 PP1 PP3 PP4 BA1

Evidence Links 1

Expert Panel

TP53 VCEP

Criteria Specification Information

Criteria Specification: *ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.1.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.188C>G variant in TP53 is a missense variant predicted to cause substitution of Alanine by Glycine at amino acid 63 (p.Ala63Gly). 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 contributors). This variant has an allele frequency of 0.00001525 (18/1180022 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 functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 29979965, 30224644). Computational predictor scores (BayesDel = -0.156; Align GVGD Class C0) are below the recommended thresholds (BayesDel ≤ -0.008 and an Align GVGD Class ≤ 55), evidence that does not predict a damaging effect on TP53 via protein change. Although SpliceAI predicts a weak potential splice effect, expert review suggests that there is no actual impact on the native site, and the variant is therefore considered to have no impact on splicing (BP4_Moderate). In summary, this variant meets the criteria to be classified as Likely Benign for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2_Supporting, PM2_Supporting, BS3, BP4_Moderate. (Bayesian Points: -6; VCEP specifications version 2.1; 1/16/2025)

Met criteria codes

BS3	✔	In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 29979965, 30224644). Predicted functional by TP53_PROF PubMed:35043155
PM2_Supporting	✔	This variant has an allele frequency of 0.00001525 (18/1180022 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).
BP4	✔	BP4_MODERATE Computational predictor scores (BayesDel = -0.156; Align GVGD Class C0) are below the recommended thresholds (BayesDel ≤ -0.008 and an Align GVGD Class ≤ 55), evidence that does not predict a damaging effect on TP53 via protein change. Although SpliceAI predicts a weak potential splice effect, expert review suggests that there is no actual impact on the native site, and the variant is therefore considered to have no impact on splicing (BP4_Moderate).
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 contributors).

Not Met criteria codes

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
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.Ala63Val, p.Ala63Thr) in the same codon have been reported (ClinVar Variation IDs: 182922, 231015). However, these variants have not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PM5 not met).
PM6	✖	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

PS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	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
PP3	✖	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

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.6(TP53):c.188C>G (p.Ala6...	Likely Benign	Li-Fraumeni Syndrome	2025-01-16	2.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.1.0	TP53
View	NM_000546.6(TP53):c.188C>G (p.Ala6...	Likely Benign	Li-Fraumeni Syndrome 1	2021-09-24	1.0	-	TP53

Showing 1 to 2 of 2 rows

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