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.206C>G (p.Ala69Gly)

Version: 1.2

CA10580956

230112 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 521a9719-6db1-4bce-9eb7-cd771b563238
Approved on: 2024/8/5
Published on: 2024/8/5

HGVS expressions

NM_000546.6(TP53):c.206C>G (p.Ala69Gly)
NM_000546.6:c.206C>G
NC_000017.11:g.7676163G>C
CM000679.2:g.7676163G>C
NC_000017.10:g.7579481G>C
CM000679.1:g.7579481G>C
NC_000017.9:g.7520206G>C
NG_017013.2:g.16388C>G
ENST00000503591.2:c.206C>G
ENST00000508793.6:c.206C>G
ENST00000509690.6:c.-21-927C>G
ENST00000514944.6:c.96+219C>G
ENST00000604348.6:c.206C>G
ENST00000269305.9:c.206C>G
ENST00000269305.8:c.206C>G
ENST00000359597.8:c.206C>G
ENST00000413465.6:c.206C>G
ENST00000420246.6:c.206C>G
ENST00000445888.6:c.206C>G
ENST00000455263.6:c.206C>G
ENST00000503591.1:c.206C>G
ENST00000505014.5:n.462C>G
ENST00000508793.5:c.206C>G
ENST00000509690.5:c.-21-927C>G
ENST00000514944.5:c.96+219C>G
ENST00000604348.5:c.206C>G
ENST00000610292.4:c.89C>G
ENST00000610538.4:c.89C>G
ENST00000615910.4:c.206C>G
ENST00000617185.4:c.206C>G
ENST00000619485.4:c.89C>G
ENST00000620739.4:c.89C>G
ENST00000622645.4:c.89C>G
ENST00000635293.1:c.89C>G
NM_000546.5:c.206C>G
NM_001126112.2:c.206C>G
NM_001126113.2:c.206C>G

NM_001126114.2:c.206C>G
NM_001126118.1:c.89C>G
NM_001276695.1:c.89C>G
NM_001276696.1:c.89C>G
NM_001276760.1:c.89C>G
NM_001276761.1:c.89C>G
NM_001276695.2:c.89C>G
NM_001276696.2:c.89C>G
NM_001276760.2:c.89C>G
NM_001276761.2:c.89C>G
NM_001126112.3:c.206C>G
NM_001126113.3:c.206C>G
NM_001126114.3:c.206C>G
NM_001126118.2:c.89C>G
NM_001276695.3:c.89C>G
NM_001276696.3:c.89C>G
NM_001276760.3:c.89C>G
NM_001276761.3:c.89C>G

Uncertain Significance

Met criteria codes 2

PM2_Supporting BP4

Not Met criteria codes 13

PM1 PM5 BA1 BS1 BS4 BS3 BS2 PS1 PS2 PS3 PS4 PP1 PP4

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.206C>G variant in TP53 is a missense variant predicted to cause substitution of alanine by glycine at amino acid 69 (p.Ala69Gly). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Computational predictor scores (BayesDel = -0.1612; 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. SpliceAI predicts that the variant has no impact on splicing (BP4_Moderate). Due to conflicting evidence, this variant is classified as a variant of unknown significance for Li Fraumeni Syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PM2_Supporting, BP4_Moderate. (Bayesian Points: -1; VCEP specifications version v2.0; 7/24/2024)

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
BP4	✔	BP4 MODERATE APPLIED Computational predictor scores (BayesDel = -0.1612; 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. SpliceAI predicts that the variant has no impact on splicing (BP4_Moderate).

Not Met criteria codes

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	✖	3 different missense variants (c.206C>T, p.Ala69Val ; c.205G>C, p.Ala69Pro ; c.205G>A, p.Ala69Thr) in the same codon have been reported (ClinVar Variation IDs: 528260, 919370 575773). 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).
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
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
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
PP4	✖	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.206C>G (p.Ala6…	Uncertain Significance	Li-Fraumeni Syndrome	2024-08-05	1.2	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0	TP53
View	NM_000546.6(TP53):c.206C>G (p.Ala6…	Uncertain Significance	Li-Fraumeni Syndrome	2024-08-05	1.1	-	TP53
View	NM_000546.5(TP53):c.206C>G (p.Ala6…	Uncertain Significance	Li-Fraumeni Syndrome	2020-01-24	1.0	-	TP53

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