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.1009C>G (p.Arg337Gly)

Version: 1.0

CA10583674

237938 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 51843582-881e-436c-b252-79aa7face271
Approved on: 2025/5/7
Published on: 2025/7/18

HGVS expressions

NM_000546.6:c.1009C>G
NM_000546.6(TP53):c.1009C>G (p.Arg337Gly)
NC_000017.11:g.7670700G>C
CM000679.2:g.7670700G>C
NC_000017.10:g.7574018G>C
CM000679.1:g.7574018G>C
NC_000017.9:g.7514743G>C
NG_017013.2:g.21851C>G
ENST00000503591.2:c.1009C>G
ENST00000508793.6:c.1009C>G
ENST00000509690.6:c.613C>G
ENST00000514944.6:c.730C>G
ENST00000604348.6:c.988C>G
ENST00000269305.9:c.1009C>G
ENST00000269305.8:c.1009C>G
ENST00000359597.8:c.993+2835C>G
ENST00000413465.6:c.782+3481C>G
ENST00000420246.6:c.*116C>G
ENST00000445888.6:c.1009C>G
ENST00000455263.6:c.*28C>G
ENST00000504290.5:c.*28C>G
ENST00000504937.5:c.613C>G
ENST00000510385.5:c.*116C>G
ENST00000576024.1:c.54-1010C>G
ENST00000610292.4:c.892C>G
ENST00000610538.4:c.*28C>G
ENST00000610623.4:c.*28C>G
ENST00000615910.4:c.976C>G
ENST00000617185.4:c.*116C>G
ENST00000618944.4:c.*116C>G
ENST00000619186.4:c.532C>G
ENST00000619485.4:c.892C>G
ENST00000620739.4:c.892C>G
ENST00000622645.4:c.*116C>G
ENST00000635293.1:c.892C>G
NM_000546.5:c.1009C>G
NM_001126112.2:c.1009C>G

NM_001126113.2:c.*28C>G
NM_001126114.2:c.*116C>G
NM_001126115.1:c.613C>G
NM_001126116.1:c.*116C>G
NM_001126117.1:c.*28C>G
NM_001126118.1:c.892C>G
NM_001276695.1:c.*28C>G
NM_001276696.1:c.*116C>G
NM_001276697.1:c.532C>G
NM_001276698.1:c.*116C>G
NM_001276699.1:c.*28C>G
NM_001276760.1:c.892C>G
NM_001276761.1:c.892C>G
NM_001276695.2:c.*28C>G
NM_001276696.2:c.*116C>G
NM_001276697.2:c.532C>G
NM_001276698.2:c.*116C>G
NM_001276699.2:c.*28C>G
NM_001276760.2:c.892C>G
NM_001276761.2:c.892C>G
NM_001126112.3:c.1009C>G
NM_001126113.3:c.*28C>G
NM_001126114.3:c.*116C>G
NM_001126115.2:c.613C>G
NM_001126116.2:c.*116C>G
NM_001126117.2:c.*28C>G
NM_001126118.2:c.892C>G
NM_001276695.3:c.*28C>G
NM_001276696.3:c.*116C>G
NM_001276697.3:c.532C>G
NM_001276698.3:c.*116C>G
NM_001276699.3:c.*28C>G
NM_001276760.3:c.892C>G
NM_001276761.3:c.892C>G

Likely Pathogenic

Met criteria codes 5

PM5_Supporting PM2_Supporting BP4 PP4 PS3

Not Met criteria codes 10

BA1 BS2 BS1 BS4 BS3 PP1 PP3 PM1 PS2 PS4

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 2.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6(TP53):c.1009C>G variant in TP53 is a missense variant predicted to cause substitution of arginine by glycine at amino acid 337 (p.Arg337Gly). This variant has an allele frequency of 0.000001545 (1/647194 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has no more than one allele per non-bottleneck subpopulation (PM2_Supporting). This variant received a total of 0.5 point in one proband. (PS4 not met; Internal lab contributors). At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, Internal lab contributor). 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 (PS3; PMIDs: 12826609, 30224644, 29979965). Computational predictor scores (BayesDel = 0.157822; Align GVGD Class C35) are below the recommended thresholds (BayesDel < 0.16 and > -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). Three missense variants (p.Arg337Ser, p.Arg337Pro, p.Arg337Leu) in the same codon have been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications.(PM5_Supporting). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS3, BP4, PM2_Supporting, PM5_Supporting, PP4. (Bayesian Points: 6; VCEP specifications version 2.3)

Met criteria codes

PM5_Supporting	✔	Three missense variants (p.Arg337Ser, p.Arg337Pro, p.Arg337Leu), in the same codon have been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications.(PM5_Supporting).
PM2_Supporting	✔	This variant has an allele frequency of 0.000001545 (1/647194 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has no more than one allele per non-bottleneck subpopulation (PM2_Supporting).
BP4	✔	Computational predictor scores (BayesDel = 0.157822; Align GVGD Class C35) are below the recommended thresholds (BayesDel < 0.16 and > -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).
PP4	✔	At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, Internal lab contributor).
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 (PS3; PMIDs: 12826609, 30224644, 29979965).

Not Met criteria codes

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
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
PM1	✖	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
PS4	✖	This variant received a total of 0.5 point in one proband. (PS4 not met; Internal lab contributors).

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.1009C>G (p.Arg...	Likely Pathogenic	Li-Fraumeni Syndrome	2025-07-18	1.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.3.0	TP53

Showing 1 to 1 of 1 rows

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