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.1010G>C (p.Arg337Pro)

Version: 1.0

CA000014

177879 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: a4a36153-1d09-4853-abdd-c07a6341e1fb
Approved on: 2025-05-07
Published on: 2025-07-18

HGVS expressions

NM_000546.6:c.1010G>C
NM_000546.6(TP53):c.1010G>C (p.Arg337Pro)
NC_000017.11:g.7670699C>G
CM000679.2:g.7670699C>G
NC_000017.10:g.7574017C>G
CM000679.1:g.7574017C>G
NC_000017.9:g.7514742C>G
NG_017013.2:g.21852G>C
ENST00000503591.2:c.1010G>C
ENST00000508793.6:c.1010G>C
ENST00000509690.6:c.614G>C
ENST00000514944.6:c.731G>C
ENST00000604348.6:c.989G>C
ENST00000269305.9:c.1010G>C
ENST00000269305.8:c.1010G>C
ENST00000359597.8:c.993+2836G>C
ENST00000413465.6:c.782+3482G>C
ENST00000420246.6:c.*117G>C
ENST00000445888.6:c.1010G>C
ENST00000455263.6:c.*29G>C
ENST00000504290.5:c.*29G>C
ENST00000504937.5:c.614G>C
ENST00000510385.5:c.*117G>C
ENST00000576024.1:c.54-1009G>C
ENST00000610292.4:c.893G>C
ENST00000610538.4:c.*29G>C
ENST00000610623.4:c.*29G>C
ENST00000615910.4:c.977G>C
ENST00000617185.4:c.*117G>C
ENST00000618944.4:c.*117G>C
ENST00000619186.4:c.533G>C
ENST00000619485.4:c.893G>C
ENST00000620739.4:c.893G>C
ENST00000622645.4:c.*117G>C
ENST00000635293.1:c.893G>C
NM_000546.5:c.1010G>C
NM_001126112.2:c.1010G>C

NM_001126113.2:c.*29G>C
NM_001126114.2:c.*117G>C
NM_001126115.1:c.614G>C
NM_001126116.1:c.*117G>C
NM_001126117.1:c.*29G>C
NM_001126118.1:c.893G>C
NM_001276695.1:c.*29G>C
NM_001276696.1:c.*117G>C
NM_001276697.1:c.533G>C
NM_001276698.1:c.*117G>C
NM_001276699.1:c.*29G>C
NM_001276760.1:c.893G>C
NM_001276761.1:c.893G>C
NM_001276695.2:c.*29G>C
NM_001276696.2:c.*117G>C
NM_001276697.2:c.533G>C
NM_001276698.2:c.*117G>C
NM_001276699.2:c.*29G>C
NM_001276760.2:c.893G>C
NM_001276761.2:c.893G>C
NM_001126112.3:c.1010G>C
NM_001126113.3:c.*29G>C
NM_001126114.3:c.*117G>C
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NM_001126116.2:c.*117G>C
NM_001126117.2:c.*29G>C
NM_001126118.2:c.893G>C
NM_001276695.3:c.*29G>C
NM_001276696.3:c.*117G>C
NM_001276697.3:c.533G>C
NM_001276698.3:c.*117G>C
NM_001276699.3:c.*29G>C
NM_001276760.3:c.893G>C
NM_001276761.3:c.893G>C

Likely Pathogenic

Met criteria codes 6

PP3 PM5_Supporting PM1_Supporting PS2_Supporting PM2_Supporting PS3

Not Met criteria codes 7

PP1 PP4 BS2 BS4 BS3 BP4 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.1010G>C variant in TP53 is a missense variant predicted to cause substitution of arginine by proline at amino acid 337 (p.Arg337Pro). This variant received a total of 0.5 points across 1 proband and therefore PS4 cannot be applied (PS4 not met; PMID: 25584008). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in an individual with a moderately LFS-associated cancer totaling 1 phenotype point (PS2_Supporting; Internal contributor). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). 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). This variant has 3 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). Computational predictor scores (BayesDel = 0.407328, Align GVGD = Class C25) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3). Another missense variant (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, PP3, PS2_Supporting, PM1_Supporting, PM2_Supporting, PM5_Supporting. (Bayesian Points: 9; VCEP specifications version 2.3)

Met criteria codes

PP3	✔	Computational predictor scores (BayesDel = 0.407328, Align GVGD = Class C25) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3).
PM5_Supporting	✔	Another missense variant (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).
PM1_Supporting	✔	This variant has 3 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).
PS2_Supporting	✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in an individual with a moderately LFS-associated cancer totaling 1 phenotype point (PS2_Supporting; Internal contributor).
PM2_Supporting	✔	This variant has an allele frequency of 0.000002681 (4/1491942 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).
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

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

BS2		✖	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
BP4		✖	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 proband and therefore PS4 cannot be applied (PS4 not met; PMID: 25584008).

Curation History

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