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Variant: NM_000546.6(TP53):c.848G>C (p.Arg283Pro)

Version: 1.0

CA397836790

486555 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: f22491ae-b124-4aa0-9d49-517b9f67eee5
Approved on: 2026/4/2
Published on: 2026/4/22

HGVS expressions

NM_000546.6(TP53):c.848G>C (p.Arg283Pro)
NM_000546.6:c.848G>C
NC_000017.11:g.7673772C>G
CM000679.2:g.7673772C>G
NC_000017.10:g.7577090C>G
CM000679.1:g.7577090C>G
NC_000017.9:g.7517815C>G
NG_017013.2:g.18779G>C
ENST00000503591.2:c.848G>C
ENST00000508793.6:c.848G>C
ENST00000509690.6:c.452G>C
ENST00000514944.6:c.569G>C
ENST00000604348.6:c.827G>C
ENST00000269305.9:c.848G>C
ENST00000269305.8:c.848G>C
ENST00000359597.8:c.848G>C
ENST00000413465.6:c.782+409G>C
ENST00000420246.6:c.848G>C
ENST00000445888.6:c.848G>C
ENST00000455263.6:c.848G>C
ENST00000504290.5:c.452G>C
ENST00000504937.5:c.452G>C
ENST00000509690.5:c.452G>C
ENST00000510385.5:c.452G>C
ENST00000610292.4:c.731G>C
ENST00000610538.4:c.731G>C
ENST00000610623.4:c.371G>C
ENST00000615910.4:c.815G>C
ENST00000617185.4:c.848G>C
ENST00000618944.4:c.371G>C
ENST00000619186.4:c.371G>C
ENST00000619485.4:c.731G>C
ENST00000620739.4:c.731G>C
ENST00000622645.4:c.731G>C
ENST00000635293.1:c.731G>C
NM_000546.5:c.848G>C
NM_001126112.2:c.848G>C

NM_001126113.2:c.848G>C
NM_001126114.2:c.848G>C
NM_001126115.1:c.452G>C
NM_001126116.1:c.452G>C
NM_001126117.1:c.452G>C
NM_001126118.1:c.731G>C
NM_001276695.1:c.731G>C
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NM_001276698.1:c.371G>C
NM_001276699.1:c.371G>C
NM_001276760.1:c.731G>C
NM_001276761.1:c.731G>C
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NM_001276699.2:c.371G>C
NM_001276760.2:c.731G>C
NM_001276761.2:c.731G>C
NM_001126112.3:c.848G>C
NM_001126113.3:c.848G>C
NM_001126114.3:c.848G>C
NM_001126115.2:c.452G>C
NM_001126116.2:c.452G>C
NM_001126117.2:c.452G>C
NM_001126118.2:c.731G>C
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NM_001276697.3:c.371G>C
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NM_001276699.3:c.371G>C
NM_001276760.3:c.731G>C
NM_001276761.3:c.731G>C

Pathogenic

Met criteria codes 5

PM1 PS3 PP3 PM2_Supporting PP4_Moderate

Not Met criteria codes 11

PM5 BA1 BS2 BS1 BS4 BS3 BP4 PS1 PS2 PS4 PP1

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 2.4.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6(TP53):c.848G>C variant in TP53 is a missense variant predicted to cause substitution of arginine by proline at amino acid 283 (p.Arg283Pro). Although this variant has been observed in germline cases, to our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met; PMID: 35974385, Internal lab contributors). At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, ClinVar GTRs, Internal lab 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 by the majority of available assays indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965, 39774325). This variant has 27 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 (≥ 10 somatic occurrences, PMID: 30311369) (PM1). Computational predictor scores (BayesDel = 0.272243; Align GVGD = Class C35) 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). In summary, this variant meets the criteria to be classified as Pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PP4_Moderate, PS3, PM1, PP3, PM2_supporting. (Bayesian Points: 10; VCEP specifications version 2.4)

Met criteria codes

PM1	✔	This variant has 27 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 (≥ 10 somatic occurrences, PMID: 30311369) (PM1).
PS3	✔	In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity by the majority of available assays indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965, 39774325).
PP3	✔	Computational predictor scores (BayesDel = 0.272243; Align GVGD = Class C35) 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).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP4_Moderate	✔	At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, ClinVar GTRs, Internal lab contributor).

Not Met criteria codes

PM5	✖	1 different missense variant (p.Arg283His) with a Grantham score equal to or less than the current variant in the same codon has been reported (ClinVar Variation IDs: 142324). However, the variant has not yet been curated to determine if it would be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PM5 not evaluated).
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
BP4		✖	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
PS4		✖	Although this variant has been observed in germline cases, to our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met; PMID: 35974385, Internal lab contributors).
PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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