

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

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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
NM_001276696.1:c.731G>C
NM_001276697.1:c.371G>C
NM_001276698.1:c.371G>C
NM_001276699.1:c.371G>C
NM_001276760.1:c.731G>C
NM_001276761.1:c.731G>C
NM_001276695.2:c.731G>C
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NM_001276697.2:c.371G>C
NM_001276698.2:c.371G>C
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
NM_001276695.3:c.731G>C
NM_001276696.3:c.731G>C
NM_001276697.3:c.371G>C
NM_001276698.3:c.371G>C
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
- PP4_Moderate
- PP3
- PM2_Supporting

Not Met criteria codes 11

- PM5
- BS2
- BS1
- BS4
- BS3
- PS1
- PS2
- PS4
- BP4
- BA1
- 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).
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).
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).

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).
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
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).
BP4			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
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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