

Variant: *NM_000546.6(TP53):c.412G>C (p.Ala138Pro)*

Version: 1.0

CA000166 [↗](#)

12376 (ClinVar) [↗](#)

Gene: TP53 ([HGNC:7157](#))

Condition: Li-Fraumeni syndrome ([MONDO:0018875](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 71e00d77-684f-44ee-8a90-9eba8ffcea8e

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HGVS expressions

NM_000546.6(TP53):c.412G>C (p.Ala138Pro)

NM_000546.6:c.412G>C

NC_000017.11:g.7675200C>G

CM000679.2:g.7675200C>G

NC_000017.10:g.7578518C>G

CM000679.1:g.7578518C>G

NC_000017.9:g.7519243C>G

NG_017013.2:g.17351G>C

ENST00000503591.2:c.412G>C

ENST00000508793.6:c.412G>C

ENST00000509690.6:c.16G>C

ENST00000514944.6:c.133G>C

ENST00000604348.6:c.391G>C

ENST00000269305.9:c.412G>C

ENST00000269305.8:c.412G>C

ENST00000359597.8:c.412G>C

ENST00000413465.6:c.412G>C

ENST00000420246.6:c.412G>C

ENST00000445888.6:c.412G>C

ENST00000455263.6:c.412G>C

ENST00000504290.5:c.16G>C

ENST00000504937.5:c.16G>C

ENST00000505014.5:n.668G>C

ENST00000508793.5:c.412G>C

ENST00000509690.5:c.16G>C

ENST00000510385.5:c.16G>C

ENST00000514944.5:c.133G>C

ENST00000604348.5:c.391G>C

ENST00000610292.4:c.295G>C

ENST00000610538.4:c.295G>C

ENST00000610623.4:c.-66G>C

ENST00000615910.4:c.379G>C

ENST00000617185.4:c.412G>C

ENST00000618944.4:c.-66G>C

ENST00000619186.4:c.-66G>C

ENST00000619485.4:c.295G>C

ENST00000620739.4:c.295G>C

	ENST00000622645.4:c.295G>C ENST00000635293.1:c.295G>C NM_000546.5:c.412G>C NM_001126112.2:c.412G>C NM_001126113.2:c.412G>C NM_001126114.2:c.412G>C NM_001126115.1:c.16G>C NM_001126116.1:c.16G>C NM_001126117.1:c.16G>C NM_001126118.1:c.295G>C NM_001276695.1:c.295G>C NM_001276696.1:c.295G>C NM_001276697.1:c.-66G>C NM_001276698.1:c.-66G>C NM_001276699.1:c.-66G>C NM_001276760.1:c.295G>C NM_001276761.1:c.295G>C NM_001276695.2:c.295G>C NM_001276696.2:c.295G>C NM_001276697.2:c.-66G>C NM_001276698.2:c.-66G>C NM_001276699.2:c.-66G>C NM_001276760.2:c.295G>C NM_001276761.2:c.295G>C NM_001126112.3:c.412G>C NM_001126113.3:c.412G>C NM_001126114.3:c.412G>C NM_001126115.2:c.16G>C NM_001126116.2:c.16G>C NM_001126117.2:c.16G>C NM_001126118.2:c.295G>C NM_001276695.3:c.295G>C NM_001276696.3:c.295G>C NM_001276697.3:c.-66G>C NM_001276698.3:c.-66G>C NM_001276699.3:c.-66G>C NM_001276760.3:c.295G>C NM_001276761.3:c.295G>C
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Likely Pathogenic

Met criteria codes 5

- PP4_Moderate
- PM2_Supporting
- PS4_Supporting
- PS3
- PP3

Not Met criteria codes 18

- PVS1
- BS1
- BS4
- BS3
- BP5
- BP7
- BP4
- BP3
- BP1
- BP2
- PS2
- BA1
- PP1
- PP2
- PM6
- PM1
- PM3
- PM4

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](#)

TP53 VCEP

The NM_000546.6: c.412G>C variant in TP53 is a missense variant predicted to cause substitution of alanine by proline at amino acid 138 (p.Ala138Pro). This variant has been reported in 1 proband/family meeting Classic LFS criteria. Based on this evidence, this variant scores 1 total points meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMID: 9569035). 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, Internal lab contributors). 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). Computational predictor scores (BayesDel = 0.5846; Align GVGD = Class 25) 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 likely pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS3, PP3, PM2_supporting, PS4_supporting, PP4_moderate. (Bayesian Points: 9; VCEP specifications version 2.3).

Met criteria codes

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, Internal lab contributors).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS4_Supporting			This variant has been reported in 1 unrelated probands/families meeting Classic LFS criteria. Based on this evidence, this variant scores 1 total points meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMID: 9569035).
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).
PP3			Computational predictor scores (BayesDel = 0.5846; Align GVGD = Class 25) 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).

Not Met criteria codes

PVS1			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
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			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
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			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
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
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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).
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 



 

 

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