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.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
Approved on: 2025/6/5
Published on: 2025/7/18

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
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NM_001276698.3:c.-66G>C
NM_001276699.3:c.-66G>C
NM_001276760.3:c.295G>C
NM_001276761.3:c.295G>C

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PS4_Supporting PP4_Moderate PS3

Not Met criteria codes 18

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

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: 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

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
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).
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).
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).
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
PP2	✖	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

PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	ℹ	✖	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
BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	ℹ	✖	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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	ℹ	✖	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

Curation History

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