Variant: NM_000546.6(TP53):c.412G>A (p.Ala138Thr)

Version: 1.0

CA397842713

1053218 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5cd32b5f-8df0-4db8-9bce-d67d3859a287
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HGVS expressions

NM_000546.6:c.412G>A
NM_000546.6(TP53):c.412G>A (p.Ala138Thr)
NC_000017.11:g.7675200C>T
CM000679.2:g.7675200C>T
NC_000017.10:g.7578518C>T
CM000679.1:g.7578518C>T
NC_000017.9:g.7519243C>T
NG_017013.2:g.17351G>A
ENST00000503591.2:c.412G>A
ENST00000508793.6:c.412G>A
ENST00000509690.6:c.16G>A
ENST00000514944.6:c.133G>A
ENST00000604348.6:c.391G>A
ENST00000269305.9:c.412G>A
ENST00000269305.8:c.412G>A
ENST00000359597.8:c.412G>A
ENST00000413465.6:c.412G>A
ENST00000420246.6:c.412G>A
ENST00000445888.6:c.412G>A
ENST00000455263.6:c.412G>A
ENST00000504290.5:c.16G>A
ENST00000504937.5:c.16G>A
ENST00000505014.5:n.668G>A
ENST00000508793.5:c.412G>A
ENST00000509690.5:c.16G>A
ENST00000510385.5:c.16G>A
ENST00000514944.5:c.133G>A
ENST00000604348.5:c.391G>A
ENST00000610292.4:c.295G>A
ENST00000610538.4:c.295G>A
ENST00000610623.4:c.-66G>A
ENST00000615910.4:c.379G>A
ENST00000617185.4:c.412G>A
ENST00000618944.4:c.-66G>A
ENST00000619186.4:c.-66G>A
ENST00000619485.4:c.295G>A
ENST00000620739.4:c.295G>A

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

Uncertain Significance

Met criteria codes 5

PM5_Supporting PP3 PP4 BS3_Supporting PM2_Supporting

Not Met criteria codes 21

BA1 BP5 BP7 BP4 BP3 BP1 BP2 BS1 BS4 BS2 PP1 PP2 PS1 PS2 PS3 PS4 PM1 PM3 PM4 PM6 PVS1

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>A variant in TP53 is a missense variant predicted to cause substitution of alanine by threonine at amino acid 138 (p.Ala138Thr). To our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3_Supporting; PMIDs: 12826609, 29979965, 30224644, [16007150]). Computational predictor scores (BayesDel = 0.4548; Align GVGD = Class 55) 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 (c.412G>C (p.Ala138Pro)) (ClinVar Variation ID: 12376), in the same codon have been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications (PM5_Supporting). At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, Internal lab contributor). In summary, this variant meets the criteria to be classified as of uncertain significance for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS3_supporting, PP3, PM2_supporting, PM5_supporting, PP4. (Bayesian Points: 3; VCEP specifications version 2.3)

Met criteria codes

PM5_Supporting	✔	Another missense variant (c.412G>C (p.Ala138Pro)) (ClinVar Variation ID: 12376), in the same codon have been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications (PM5_Supporting).
PP3	✔	Computational predictor scores (BayesDel = 0.4548; Align GVGD = Class 55) 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).
PP4	✔	At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, ClinVar GTRs, Internal lab contributors).
BS3_Supporting	✔	In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3_Supporting; PMIDs: 12826609, 29979965, 30224644, [16007150]).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

BA1	✖	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
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
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	ℹ	✖	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
PS1	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
PS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	ℹ	✖	To our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met).
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
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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