Variant: NM_000546.6(TP53):c.413C>A (p.Ala138Asp)

Version: 1.0

CA397842699

528270 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 13274ad3-33eb-4e3f-a51e-b8200de80394
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HGVS expressions

NM_000546.6:c.413C>A
NM_000546.6(TP53):c.413C>A (p.Ala138Asp)
NC_000017.11:g.7675199G>T
CM000679.2:g.7675199G>T
NC_000017.10:g.7578517G>T
CM000679.1:g.7578517G>T
NC_000017.9:g.7519242G>T
NG_017013.2:g.17352C>A
ENST00000503591.2:c.413C>A
ENST00000508793.6:c.413C>A
ENST00000509690.6:c.17C>A
ENST00000514944.6:c.134C>A
ENST00000604348.6:c.392C>A
ENST00000269305.9:c.413C>A
ENST00000269305.8:c.413C>A
ENST00000359597.8:c.413C>A
ENST00000413465.6:c.413C>A
ENST00000420246.6:c.413C>A
ENST00000445888.6:c.413C>A
ENST00000455263.6:c.413C>A
ENST00000504290.5:c.17C>A
ENST00000504937.5:c.17C>A
ENST00000505014.5:n.669C>A
ENST00000508793.5:c.413C>A
ENST00000509690.5:c.17C>A
ENST00000510385.5:c.17C>A
ENST00000514944.5:c.134C>A
ENST00000604348.5:c.392C>A
ENST00000610292.4:c.296C>A
ENST00000610538.4:c.296C>A
ENST00000610623.4:c.-65C>A
ENST00000615910.4:c.380C>A
ENST00000617185.4:c.413C>A
ENST00000618944.4:c.-65C>A
ENST00000619186.4:c.-65C>A
ENST00000619485.4:c.296C>A
ENST00000620739.4:c.296C>A

ENST00000622645.4:c.296C>A
ENST00000635293.1:c.296C>A
NM_000546.5:c.413C>A
NM_001126112.2:c.413C>A
NM_001126113.2:c.413C>A
NM_001126114.2:c.413C>A
NM_001126115.1:c.17C>A
NM_001126116.1:c.17C>A
NM_001126117.1:c.17C>A
NM_001126118.1:c.296C>A
NM_001276695.1:c.296C>A
NM_001276696.1:c.296C>A
NM_001276697.1:c.-65C>A
NM_001276698.1:c.-65C>A
NM_001276699.1:c.-65C>A
NM_001276760.1:c.296C>A
NM_001276761.1:c.296C>A
NM_001276695.2:c.296C>A
NM_001276696.2:c.296C>A
NM_001276697.2:c.-65C>A
NM_001276698.2:c.-65C>A
NM_001276699.2:c.-65C>A
NM_001276760.2:c.296C>A
NM_001276761.2:c.296C>A
NM_001126112.3:c.413C>A
NM_001126113.3:c.413C>A
NM_001126114.3:c.413C>A
NM_001126115.2:c.17C>A
NM_001126116.2:c.17C>A
NM_001126117.2:c.17C>A
NM_001126118.2:c.296C>A
NM_001276695.3:c.296C>A
NM_001276696.3:c.296C>A
NM_001276697.3:c.-65C>A
NM_001276698.3:c.-65C>A
NM_001276699.3:c.-65C>A
NM_001276760.3:c.296C>A
NM_001276761.3:c.296C>A

Uncertain Significance

Met criteria codes 4

PM2_Supporting PM5_Supporting PP3_Moderate BS3_Supporting

Not Met criteria codes 18

BA1 BS1 BS4 BS2 BP7 BP4 BP3 BP1 PS1 PS2 PS3 PS4 PP1 PP2 PP4 PVS1 PM1 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**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.413C>A variant in TP53 is a missense variant predicted to cause substitution of alanine by asparginine at amino acid 138 (p.Ala138Asp). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant received a total of 0.5 points across one proband. (PS4 not met; Internal lab contributor). 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). Computational predictor scores (BayesDel = 0.5405; Align GVGD = Class 65) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate). Another missense variant (c.412G>C (p.Ala138Pro)) (ClinVar Variation ID: 12376), in the same codon has been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications (PM5_Supporting). In summary, this variant meets the criteria to be classified as a variant of uncertain significance for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PM2_supporting, BS3_supporting, PP3_moderate, PM5_Supporting. (Bayesian Points: 3; VCEP specifications version 2.3)

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
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_Moderate	✔	Computational predictor scores (BayesDel = 0.5405; Align GVGD = Class 65) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate).
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).

Not Met criteria codes

BA1	✖	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
BS2	✖	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
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
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4		✖	This variant received a total of 0.5 points across one proband. (PS4 not met; Internal lab contributor).
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
PP4		✖	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
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).
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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