Variant: NM_001276761.1:c.311T>C

Version: 2.0

CA397842518

804214 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 96976462-a14e-41e1-9dc6-73aa6108c844
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HGVS expressions

NM_001276761.1:c.311T>C
NC_000017.11:g.7675184A>G
CM000679.2:g.7675184A>G
NC_000017.10:g.7578502A>G
CM000679.1:g.7578502A>G
NC_000017.9:g.7519227A>G
NG_017013.2:g.17367T>C
ENST00000503591.2:c.428T>C
ENST00000508793.6:c.428T>C
ENST00000509690.6:c.32T>C
ENST00000514944.6:c.149T>C
ENST00000604348.6:c.407T>C
ENST00000269305.9:c.428T>C
ENST00000269305.8:c.428T>C
ENST00000359597.8:c.428T>C
ENST00000413465.6:c.428T>C
ENST00000420246.6:c.428T>C
ENST00000445888.6:c.428T>C
ENST00000455263.6:c.428T>C
ENST00000504290.5:c.32T>C
ENST00000504937.5:c.32T>C
ENST00000505014.5:n.684T>C
ENST00000508793.5:c.428T>C
ENST00000509690.5:c.32T>C
ENST00000510385.5:c.32T>C
ENST00000514944.5:c.149T>C
ENST00000604348.5:c.407T>C
ENST00000610292.4:c.311T>C
ENST00000610538.4:c.311T>C
ENST00000610623.4:c.-50T>C
ENST00000615910.4:c.395T>C
ENST00000617185.4:c.428T>C
ENST00000618944.4:c.-50T>C
ENST00000619186.4:c.-50T>C
ENST00000619485.4:c.311T>C
ENST00000620739.4:c.311T>C
ENST00000622645.4:c.311T>C

ENST00000635293.1:c.311T>C
NM_000546.5:c.428T>C
NM_001126112.2:c.428T>C
NM_001126113.2:c.428T>C
NM_001126114.2:c.428T>C
NM_001126115.1:c.32T>C
NM_001126116.1:c.32T>C
NM_001126117.1:c.32T>C
NM_001126118.1:c.311T>C
NM_001276695.1:c.311T>C
NM_001276696.1:c.311T>C
NM_001276697.1:c.-50T>C
NM_001276698.1:c.-50T>C
NM_001276699.1:c.-50T>C
NM_001276760.1:c.311T>C
NM_001276695.2:c.311T>C
NM_001276696.2:c.311T>C
NM_001276697.2:c.-50T>C
NM_001276698.2:c.-50T>C
NM_001276699.2:c.-50T>C
NM_001276760.2:c.311T>C
NM_001276761.2:c.311T>C
NM_000546.6:c.428T>C
NM_001126112.3:c.428T>C
NM_001126113.3:c.428T>C
NM_001126114.3:c.428T>C
NM_001126115.2:c.32T>C
NM_001126116.2:c.32T>C
NM_001126117.2:c.32T>C
NM_001126118.2:c.311T>C
NM_001276695.3:c.311T>C
NM_001276696.3:c.311T>C
NM_001276697.3:c.-50T>C
NM_001276698.3:c.-50T>C
NM_001276699.3:c.-50T>C
NM_001276760.3:c.311T>C
NM_001276761.3:c.311T>C

Pathogenic

Met criteria codes 5

PM2_Supporting PM1_Supporting PS2 PS3 PP3

Not Met criteria codes 9

BS2 BS1 BS3 BP4 PS1 PS4 BA1 PP4 PM5

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 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.428T>C variant in TP53 is a missense variant predicted to cause substitution of Valine by Alanine at amino acid 143 (p.Val143Ala). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual and as a de novo occurrence with unconfirmed parental relationships in 1 individual with an LFS-associated cancer totaling 6 phenotype points (PS2; PMID: 19701813, 25318593). 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 = 0.1806; Align GVGD = Class C25) 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). This variant has 7 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspot critical functional domain by the Clingen TP53 VCEP (2-9 somatic occurrences, PMID: 30311369) (PM1_Supporting). 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: PS2, PM2_Supporting, PS3, PP3, PM1_Supporting. (Bayesian Points: 11; VCEP specifications version 2.0; 7/24/2024).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PM1_Supporting	✔	This variant has 7 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspotcritical functional domain by the Clingen TP53 VCEP (2-9 somatic occurrences, PMID: 30311369) (PM1_Supporting).
PS2	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual and as a de novo occurrence with unconfirmed parental relationships in 1 individual with an LFS-associated cancer totaling 6 phenotype points (PS2; PMID: 19701813, 25318593).
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 = 0.1806; Align GVGD = Class C25) 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

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
BS3	✖	

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
PS1	✖	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 1 point across 2 unrelated probands. However, PS4 cannot be applied because these were both de novo cases counted towards PS2. (PS4 not met; PMIDs: 29070607, 19701813).
BA1	✖	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
PM5	✖	3 different missense variants (c.427G>A; p.Val143Met and c.427G>T; p.Val143Leu and c.428T>G; p.Val143Gly) in the same codon have been reported in ClinVar (Variation ID: 185729, 486556 and 486556). However, these variants have not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PM5 not met).

Curation History

Showing 1 to 2 of 2 rows