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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
Approved on: 2024/8/5
Published on: 2024/8/5

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

PM1_Supporting PM2_Supporting PS2 PS3 PP3

Not Met criteria codes 9

BA1 PM5 BS2 BS1 BS3 BP4 PS1 PS4 PP4

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

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).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_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

BA1	✖	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).

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).
PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001276761.1:c.311T>C	Pathogenic	Li-Fraumeni Syndrome	2024-08-05	2.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0	TP53
View	NM_001276761.1:c.311T>C	Likely Pathogenic	Li-Fraumeni Syndrome	2020-01-24	1.0	-	TP53

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