Variant: NM_000546.6(TP53):c.375+5G>A

Version: 1.0

CA645589233

481015 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 9f4d2b30-c424-4a1b-b116-f50eb532e233
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HGVS expressions

NM_000546.6:c.375+5G>A
NM_000546.6(TP53):c.375+5G>A
NC_000017.11:g.7675989C>T
CM000679.2:g.7675989C>T
NC_000017.10:g.7579307C>T
CM000679.1:g.7579307C>T
NC_000017.9:g.7520032C>T
NG_017013.2:g.16562G>A
ENST00000503591.2:c.375+5G>A
ENST00000508793.6:c.375+5G>A
ENST00000509690.6:c.-21-753G>A
ENST00000514944.6:c.96+393G>A
ENST00000604348.6:c.375+5G>A
ENST00000269305.9:c.375+5G>A
ENST00000269305.8:c.375+5G>A
ENST00000359597.8:c.375+5G>A
ENST00000413465.6:c.375+5G>A
ENST00000420246.6:c.375+5G>A
ENST00000445888.6:c.375+5G>A
ENST00000455263.6:c.375+5G>A
ENST00000503591.1:c.375+5G>A
ENST00000505014.5:n.631+5G>A
ENST00000508793.5:c.375+5G>A
ENST00000509690.5:c.-21-753G>A
ENST00000514944.5:c.96+393G>A
ENST00000604348.5:c.375+5G>A
ENST00000610292.4:c.258+5G>A
ENST00000610538.4:c.258+5G>A
ENST00000615910.4:c.340+36G>A
ENST00000617185.4:c.375+5G>A
ENST00000619485.4:c.258+5G>A
ENST00000620739.4:c.258+5G>A
ENST00000622645.4:c.258+5G>A
ENST00000635293.1:c.258+5G>A
NM_000546.5:c.375+5G>A
NM_001126112.2:c.375+5G>A
NM_001126113.2:c.375+5G>A

NM_001126114.2:c.375+5G>A
NM_001126118.1:c.258+5G>A
NM_001276695.1:c.258+5G>A
NM_001276696.1:c.258+5G>A
NM_001276760.1:c.258+5G>A
NM_001276761.1:c.258+5G>A
NM_001276695.2:c.258+5G>A
NM_001276696.2:c.258+5G>A
NM_001276760.2:c.258+5G>A
NM_001276761.2:c.258+5G>A
NM_001126112.3:c.375+5G>A
NM_001126113.3:c.375+5G>A
NM_001126114.3:c.375+5G>A
NM_001126118.2:c.258+5G>A
NM_001276695.3:c.258+5G>A
NM_001276696.3:c.258+5G>A
NM_001276760.3:c.258+5G>A
NM_001276761.3:c.258+5G>A

Likely Pathogenic

Met criteria codes 5

PVS1_Strong PS4_Moderate PP4_Moderate PM2_Supporting BS2_Supporting

Not Met criteria codes 4

BA1 BS1 BP4 PP3

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 c.375+5G>A intronic variant results from a G to A substitution 5 nucleotides after coding exon 3 in the TP53 gene. Splicing assay data provides experimental evidence that this variant results in RNA transcript with loss of function (PVS1_Strong (RNA); PMID:31092812). This variant has been reported in 1 family meeting Classic criteria and in 2 families meeting Revised Chompret Criteria. Based on this evidence, this variant scores 2 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; Internal contributors). This variant has been observed in 2-3 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Supporting; Internal lab contributor). 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 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: PVS1_Strong (RNA), PS4_Moderate, BS2_Supporting, PP4_Moderate, PM2_Supporting. (Bayesian Points: 8; VCEP specifications version 2.3)

Met criteria codes

PVS1_Strong	✔	Splicing assay data provides experimental evidence that this variant results in RNA transcript with loss of function (PVS1_Strong (RNA); PMID:31092812).
PS4_Moderate	✔	This variant has been reported in 1 family meeting Classic criteria and in 2 families meeting Revised Chompret Criteria. Based on this evidence, this variant scores 2 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; Internal contributors).
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).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
BS2_Supporting	✔	This variant has been observed in 2-3 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Supporting; Internal lab contributor).

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
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	PP3 should not be used in combination with PVS1 The computational splicing predictor SpliceAI gives a score of 0.9, predicting that the variant has an impact on splicing (score threshold > 0.20)

Curation History

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