Variant: NM_000546.5(TP53):c.353C>T (p.Thr118Ile)

Version: 2.0

CA16620635

419837 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: fc7cc0ba-f84e-46c8-acb3-ef170d24b394
Approved on: 2025-03-04
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HGVS expressions

NM_000546.5:c.353C>T
NM_000546.5(TP53):c.353C>T (p.Thr118Ile)
NC_000017.11:g.7676016G>A
CM000679.2:g.7676016G>A
NC_000017.10:g.7579334G>A
CM000679.1:g.7579334G>A
NC_000017.9:g.7520059G>A
NG_017013.2:g.16535C>T
ENST00000503591.2:c.353C>T
ENST00000508793.6:c.353C>T
ENST00000509690.6:c.-21-780C>T
ENST00000514944.6:c.96+366C>T
ENST00000604348.6:c.353C>T
ENST00000269305.9:c.353C>T
ENST00000269305.8:c.353C>T
ENST00000359597.8:c.353C>T
ENST00000413465.6:c.353C>T
ENST00000420246.6:c.353C>T
ENST00000445888.6:c.353C>T
ENST00000455263.6:c.353C>T
ENST00000503591.1:c.353C>T
ENST00000505014.5:n.609C>T
ENST00000508793.5:c.353C>T
ENST00000509690.5:c.-21-780C>T
ENST00000514944.5:c.96+366C>T
ENST00000604348.5:c.353C>T
ENST00000610292.4:c.236C>T
ENST00000610538.4:c.236C>T
ENST00000615910.4:c.340+9C>T
ENST00000617185.4:c.353C>T
ENST00000619485.4:c.236C>T
ENST00000620739.4:c.236C>T
ENST00000622645.4:c.236C>T
ENST00000635293.1:c.236C>T
NM_001126112.2:c.353C>T
NM_001126113.2:c.353C>T
NM_001126114.2:c.353C>T

NM_001126118.1:c.236C>T
NM_001276695.1:c.236C>T
NM_001276696.1:c.236C>T
NM_001276760.1:c.236C>T
NM_001276761.1:c.236C>T
NM_001276695.2:c.236C>T
NM_001276696.2:c.236C>T
NM_001276760.2:c.236C>T
NM_001276761.2:c.236C>T
NM_000546.6:c.353C>T
NM_001126112.3:c.353C>T
NM_001126113.3:c.353C>T
NM_001126114.3:c.353C>T
NM_001126118.2:c.236C>T
NM_001276695.3:c.236C>T
NM_001276696.3:c.236C>T
NM_001276760.3:c.236C>T
NM_001276761.3:c.236C>T

Likely Benign

Met criteria codes 4

BS2_Supporting PM2_Supporting PP3_Moderate BS3

Not Met criteria codes 11

PS1 PS2 PS3 BA1 PP1 PM1 PM6 BS1 BS4 BP4 BP2

Evidence Links 3

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.353C>T variant in TP53 is a missense variant predicted to cause substitution of threonine by isoleucine at amino acid 118 (p.Thr118Ile). 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; ClinVar SCVs: SCV000664386.6). This variant has an allele frequency of 0.0000006203 (1/1612196 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has no more than one allele per non-bottleneck subpopulation (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function(BS3; PMIDs: 12826609, 29979965, 30224644). Computational predictor scores (BayesDel = 0.3466; 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). In summary, this variant meets the criteria to be classified as likely benign for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2_Supporting, PM2_Supporting, BS3, PP3_Moderate. (Bayesian Points: -2; VCEP specifications version 2.3).

Met criteria codes

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; ClinVar SCVs: SCV000664386.6).
PM2_Supporting	✔	This variant has an allele frequency of 0.0000006203 (1/1612196 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has no more than one allele per non-bottleneck subpopulation (PM2_Supporting).
PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.3466; 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	✔	In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function(BS3; PMIDs: 12826609, 29979965, 30224644). noLOF/noDNE **PubMed:30224644** noLOF **PubMed:29979965** Functional **PubMed:12826609**

Not Met criteria codes

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
BA1	✖	Absent in gnomAD v2.1.1 (non-cancer)
PP1	✖	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).
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	Absent in gnomAD v2.1.1 (non-cancer)

BS4		✖	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
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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