

Variant: NM_000546.6(TP53):c.105G>T (p.Leu35Phe)

Version: 1.0

CA000025 [↗](#)

12371 (ClinVar) [↗](#)

Gene: TP53 ([HGNC:7157](#))

Condition: Li-Fraumeni syndrome ([MONDO:0018875](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: b73a437c-26a5-4491-8b92-edbe32570d9e

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HGVS expressions

NM_000546.6:c.105G>T

NM_000546.6(TP53):c.105G>T (p.Leu35Phe)

NC_000017.11:g.7676264C>A

CM000679.2:g.7676264C>A

NC_000017.10:g.7579582C>A

CM000679.1:g.7579582C>A

NC_000017.9:g.7520307C>A

NG_017013.2:g.16287G>T

ENST00000503591.2:c.105G>T

ENST00000508793.6:c.105G>T

ENST00000509690.6:c.-21-1028G>T

ENST00000514944.6:c.96+118G>T

ENST00000604348.6:c.105G>T

ENST00000269305.9:c.105G>T

ENST00000269305.8:c.105G>T

ENST00000359597.8:c.105G>T

ENST00000413465.6:c.105G>T

ENST00000420246.6:c.105G>T

ENST00000445888.6:c.105G>T

ENST00000455263.6:c.105G>T

ENST00000503591.1:c.105G>T

ENST00000505014.5:n.361G>T

ENST00000508793.5:c.105G>T

ENST00000509690.5:c.-21-1028G>T

ENST00000514944.5:c.96+118G>T

ENST00000604348.5:c.105G>T

ENST00000610292.4:c.-13G>T

ENST00000610538.4:c.-13G>T

ENST00000615910.4:c.105G>T

ENST00000617185.4:c.105G>T

ENST00000619485.4:c.-13G>T

ENST00000620739.4:c.-13G>T

ENST00000622645.4:c.-13G>T

ENST00000635293.1:c.-13G>T

NM_000546.5:c.105G>T

NM_001126112.2:c.105G>T

NM_001126113.2:c.105G>T

NM_001126114.2:c.105G>T
NM_001126118.1:c.-13G>T
NM_001276695.1:c.-13G>T
NM_001276696.1:c.-13G>T
NM_001276760.1:c.-13G>T
NM_001276761.1:c.-13G>T
NM_001276695.2:c.-13G>T
NM_001276696.2:c.-13G>T
NM_001276760.2:c.-13G>T
NM_001276761.2:c.-13G>T
NM_001126112.3:c.105G>T
NM_001126113.3:c.105G>T
NM_001126114.3:c.105G>T
NM_001126118.2:c.-13G>T
NM_001276695.3:c.-13G>T
NM_001276696.3:c.-13G>T
NM_001276760.3:c.-13G>T
NM_001276761.3:c.-13G>T

Uncertain Significance

Met criteria codes 2

BP4 PM2_Supporting

Not Met criteria codes 14

BA1 BS2 BS1 BS4 BS3 PS1
PS2 PS3 PS4 PP1 PP3 PP4
PM1 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.105G>T variant in TP53 is a missense variant predicted to cause substitution of leucine by phenylalanine at amino acid 35 (p.Leu35Phe). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Computational predictor scores (BayesDel = -0.078; Align GVGD Class C0) are below the recommended thresholds (BayesDel ≤ -0.008 and an Align GVGD Class ≤ 55), evidence that does not predict a damaging effect on TP53 via protein change. Although SpliceAI predicts a weak potential splice effect, expert review suggests there is no impact on the native site, and following expert review the variant is considered to have no impact on splicing. (BP4_Moderate). In summary, this variant meets the criteria to be classified as Variant of Uncertain Significance for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PM2_Supporting, BP4_Moderate. (Bayesian Points: -1; VCEP specifications version 2.0; date of approval)

Met criteria codes

BP4



BP4_MODERATE Computational predictor scores (BayesDel = -0.078; Align GVGD Class C0) are below the recommended thresholds (BayesDel ≤ -0.008 and an Align GVGD Class ≤ 55), evidence that does not predict a damaging effect on TP53 via protein change. Although SpliceAI predicts a weak potential splice effect, expert review

suggests there is no impact on the native site, and following expert review the variant is considered to have no impact on splicing. (BP4_Moderate)

PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
Not Met criteria codes			
BA1			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
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
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). Code not applied at PP3 is applied
PS1			The same amino acid change, resulting from a different nucleotide change (c.105G>C), has been reported (ClinVar Variation ID: 142562). However, this other variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PS1 not met).
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			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			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

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).
PM5			Another missense variant(c.103T>A, p.Leu35Met) in the same codon has been reported (ClinVar Variation ID: 406609). However, this variant has not yet been curated to determine if it would be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PM5 not met).

Curation History 		
		
Showing 1 to 1 of 1 rows		

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