

Variant: NM_000546.6(TP53):c.537T>A (p.His179Gln)

CA16615708 [↗](#)

406578 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 2f0057b7-4b8d-4b05-98bd-c7760ee4259c

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HGVS expressions

NM_000546.6:c.537T>A

NM_000546.6(TP53):c.537T>A (p.His179Gln)

NC_000017.11:g.7675075A>T

CM000679.2:g.7675075A>T

NC_000017.10:g.7578393A>T

CM000679.1:g.7578393A>T

NC_000017.9:g.7519118A>T

NG_017013.2:g.17476T>A

ENST00000503591.2:c.537T>A

ENST00000508793.6:c.537T>A

ENST00000509690.6:c.141T>A

ENST00000514944.6:c.258T>A

ENST00000604348.6:c.516T>A

ENST00000269305.9:c.537T>A

ENST00000269305.8:c.537T>A

ENST00000359597.8:c.537T>A

ENST00000413465.6:c.537T>A

ENST00000420246.6:c.537T>A

ENST00000445888.6:c.537T>A

ENST00000455263.6:c.537T>A

ENST00000504290.5:c.141T>A

ENST00000504937.5:c.141T>A

ENST00000505014.5:n.793T>A

ENST00000509690.5:c.141T>A

ENST00000510385.5:c.141T>A

ENST00000514944.5:c.258T>A

ENST00000574684.1:n.45T>A

ENST00000610292.4:c.420T>A

ENST00000610538.4:c.420T>A

ENST00000610623.4:c.60T>A

ENST00000615910.4:c.504T>A

ENST00000617185.4:c.537T>A

ENST00000618944.4:c.60T>A

ENST00000619186.4:c.60T>A

ENST00000619485.4:c.420T>A

ENST00000620739.4:c.420T>A

ENST00000622645.4:c.420T>A

	ENST00000635293.1:c.420T>A
	NM_000546.5:c.537T>A
	NM_001126112.2:c.537T>A
	NM_001126113.2:c.537T>A
	NM_001126114.2:c.537T>A
	NM_001126115.1:c.141T>A
	NM_001126116.1:c.141T>A
	NM_001126117.1:c.141T>A
	NM_001126118.1:c.420T>A
	NM_001276695.1:c.420T>A
	NM_001276696.1:c.420T>A
	NM_001276697.1:c.60T>A
	NM_001276698.1:c.60T>A
	NM_001276699.1:c.60T>A
	NM_001276760.1:c.420T>A
	NM_001276761.1:c.420T>A
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	NM_001276696.2:c.420T>A
	NM_001276697.2:c.60T>A
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	NM_001276761.2:c.420T>A
	NM_001126112.3:c.537T>A
	NM_001126113.3:c.537T>A
	NM_001126114.3:c.537T>A
	NM_001126115.2:c.141T>A
	NM_001126116.2:c.141T>A
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	NM_001276698.3:c.60T>A
	NM_001276699.3:c.60T>A
	NM_001276760.3:c.420T>A
	NM_001276761.3:c.420T>A

Pathogenic

Met criteria codes 6

- PM1
- PS1_Moderate
- PS3
- PP4_Moderate
- PM2_Supporting
- PS2_Moderate

Not Met criteria codes 10

- PM6
- BA1
- BS4
- BS3
- BS1
- BS2
- BP4
- PS4
- PP1
- 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 2.0.0

- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

TP53 VCEP

The NM_000546.6: c.537T>A variant in TP53 is a missense variant predicted to cause substitution of histidine by glutamine at amino acid 179 (p.His179Gln). 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). This variant has 12 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspot by the Clingen TP53 VCEP (≥ 10 somatic occurrences, PMID: 30311369). The same amino acid change (p.His179Gln), resulting from a different nucleotide change (c.537T>G) (ClinVar Variation ID: 376607; PMIDs: 18511570, 31119730), is classified as likely pathogenic for Li-Fraumeni syndrome by following the ClinGen TP53 VCEP’s specifications. Splicing prediction using SpliceAI revealed no expected impact on splicing due to either variant (PS1_Moderate). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with an LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; PMID: 19556618). 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 contributor: SCV000664423.4). This variant is absent from gnomAD v4.1.0 (PM2_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: PS3, PM1, PS1_Moderate, PS2_Moderate, PP4_Moderate, PM2_Supporting. (Bayesian Points: 13; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

PM1			This variant has 12 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspot by the Clingen TP53 VCEP (≥ 10 somatic occurrences, PMID: 30311369).
PS1_Moderate			The same amino acid change (p.His179Gln), resulting from a different nucleotide change (c.537T>G) (ClinVar Variation ID: 376607; PMIDs: 18511570, 31119730), is classified as likely pathogenic for Li-Fraumeni syndrome by following the ClinGen TP53 VCEP’s specifications. Splicing prediction using SpliceAI revealed no expected impact on splicing due to either variant (PS1_Moderate).
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).
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 contributor: SCV000664423.4).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS2_Moderate			This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with an LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; PMID: 19556618).

Not Met criteria codes

PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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BA1			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			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
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			The results from the computational predictors BayesDel and AlignGVGD do not agree, providing no evidence that correlates with a damaging or benign impact on TP53 function via protein change. Additionally, the computational splicing predictor SpliceAI predicts that the variant has no impact on splicing (score threshold ≤ 0.10) (PP3 and BP4 not met).
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			The results from the computational predictors BayesDel and AlignGVGD do not agree, providing no evidence that correlates with a damaging or benign impact on TP53 function via protein change. Additionally, the computational splicing predictor SpliceAI predicts that the variant has no impact on splicing (score threshold ≤ 0.10) (PP3 and BP4 not met).

Curation History [↗](#)



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See Report	⬆ Preferred Variant Title	⬆ Classification 	⬆ Condition	⬆ Published Date	⬆ Version 	Criteria Specification	⬆ Gene
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No matching records found

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