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

Version: 1.1

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
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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
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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_001276760.2:c.420T>A
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NM_001126112.3:c.537T>A
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NM_001126114.3:c.537T>A
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NM_001276697.3:c.60T>A
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 PP4_Moderate PS1_Moderate PS3 PS2_Moderate PM2_Supporting

Not Met criteria codes 10

PM6 BA1 BS2 BS1 BS4 BS3 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**

Evidence submitted by expert panel

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

Not Met criteria codes

PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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		✖	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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