

Variant: *NM_000546.5(TP53):c.532C>G (p.His178Asp)*

Version: 2.0

CA397841387 [↗](#)

482223 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: a1e9d7d7-42fc-4628-a8f2-f372d4d051d1

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HGVS expressions

NM_000546.5(TP53):c.532C>G (p.His178Asp)

NM_000546.5:c.532C>G

NC_000017.11:g.7675080G>C

CM000679.2:g.7675080G>C

NC_000017.10:g.7578398G>C

CM000679.1:g.7578398G>C

NC_000017.9:g.7519123G>C

NG_017013.2:g.17471C>G

ENST00000503591.2:c.532C>G

ENST00000508793.6:c.532C>G

ENST00000509690.6:c.136C>G

ENST00000514944.6:c.253C>G

ENST00000604348.6:c.511C>G

ENST00000269305.9:c.532C>G

ENST00000269305.8:c.532C>G

ENST00000359597.8:c.532C>G

ENST00000413465.6:c.532C>G

ENST00000420246.6:c.532C>G

ENST00000445888.6:c.532C>G

ENST00000455263.6:c.532C>G

ENST00000504290.5:c.136C>G

ENST00000504937.5:c.136C>G

ENST00000505014.5:n.788C>G

ENST00000509690.5:c.136C>G

ENST00000510385.5:c.136C>G

ENST00000514944.5:c.253C>G

ENST00000574684.1:n.40C>G

ENST00000610292.4:c.415C>G

ENST00000610538.4:c.415C>G

ENST00000610623.4:c.55C>G

ENST00000615910.4:c.499C>G

ENST00000617185.4:c.532C>G

ENST00000618944.4:c.55C>G

ENST00000619186.4:c.55C>G

ENST00000619485.4:c.415C>G

ENST00000620739.4:c.415C>G

ENST00000622645.4:c.415C>G

	ENST000000635293.1:c.415C>G
	NM_001126112.2:c.532C>G
	NM_001126113.2:c.532C>G
	NM_001126114.2:c.532C>G
	NM_001126115.1:c.136C>G
	NM_001126116.1:c.136C>G
	NM_001126117.1:c.136C>G
	NM_001126118.1:c.415C>G
	NM_001276695.1:c.415C>G
	NM_001276696.1:c.415C>G
	NM_001276697.1:c.55C>G
	NM_001276698.1:c.55C>G
	NM_001276699.1:c.55C>G
	NM_001276760.1:c.415C>G
	NM_001276761.1:c.415C>G
	NM_001276695.2:c.415C>G
	NM_001276696.2:c.415C>G
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	NM_001276698.2:c.55C>G
	NM_001276699.2:c.55C>G
	NM_001276760.2:c.415C>G
	NM_001276761.2:c.415C>G
	NM_000546.6:c.532C>G
	NM_001126112.3:c.532C>G
	NM_001126113.3:c.532C>G
	NM_001126114.3:c.532C>G
	NM_001126115.2:c.136C>G
	NM_001126116.2:c.136C>G
	NM_001126117.2:c.136C>G
	NM_001126118.2:c.415C>G
	NM_001276695.3:c.415C>G
	NM_001276696.3:c.415C>G
	NM_001276697.3:c.55C>G
	NM_001276698.3:c.55C>G
	NM_001276699.3:c.55C>G
	NM_001276760.3:c.415C>G
	NM_001276761.3:c.415C>G

Pathogenic

Met criteria codes 6

- PS3
- PM1_Supporting
- PM2_Supporting
- PS2_Moderate
- PP3_Moderate
- PS4_Supporting

Not Met criteria codes 12

- PS1
- PM5
- BA1
- PP1
- PP4
- PVS1
- BS2
- BS1
- BS4
- BS3
- BP4
- BP7

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.532C>G variant in TP53 is a missense variant predicted to cause substitution of histidine by aspartic acid at amino acid 178 (p.His178Asp). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with a strongly-associated LFS-associated cancers totaling 2 phenotype points (PS2_Moderate; PMID 21345075). This variant has been reported in 2 additional unrelated probands meeting revised Chompret criteria. Based on this evidence, this variant scores 1 total point meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; SCV000754561.6, SCV000667198.3). This variant has an allele frequency of 6.195e-7 (1/1614230 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). In vitro assays performed in yeast and human cells showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644). This variant has five 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 (2-9 somatic occurrences, PMID: 30311369) (PM1_Supporting). Computational predictor scores (BayesDel =0.4249); Align GVGD = Class C65) 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 pathogenic for Li Fraumeni Syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS2_Moderate, PS4_Supporting, PM2_Supporting, PS3, PM1_Supporting, PP3_Moderate. (Bayesian Points: 11; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

PS3			In vitro assays performed in yeast and/or human cells lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644).
PM1_Supporting			This variant has five 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 (2-9 somatic occurrences, PMID: 30311369) (PM1_Supporting).
PM2_Supporting			This variant has an allele frequency of 6.195e-7 (1/1614230 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
PS2_Moderate			This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with a strongly-associated LFS-associated cancers totaling 2 phenotype points (PS2_Moderate; PMID 21345075).
PP3_Moderate			Computational predictor scores (BayesDel =0.4249); Align GVGD = Class C65) 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).
PS4_Supporting			This variant has been reported in 2 additional unrelated probands meeting revised Chompret criteria. Based on this evidence, this variant scores 1 total point meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; SCV000754561.6, SCV000667198.3).

Not Met criteria codes

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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PM5			Four different missense variants (c.534C>G, p.His178Gln; c.534C>A, p.His178Gln; c.533A>C, p.His178Pro; c.532C>A, (p.His178Asn) in the same codon have been reported (ClinVar Variation IDs: 947223, 575702, 485030, 421546). However, the variants have not yet been curated to determine if they would be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PM5 not evaluated).
BA1			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
PP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			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			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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