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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
Approved on: 2024/8/5
Published on: 2024/8/5

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

ENST00000635293.1: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
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NM_001276699.1:c.55C>G
NM_001276760.1:c.415C>G
NM_001276761.1:c.415C>G
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NM_001276760.2:c.415C>G
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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

PM1_Supporting PS2_Moderate PP3_Moderate PM2_Supporting PS3 PS4_Supporting

Not Met criteria codes 12

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

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.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

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).
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).
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).
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).
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

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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).
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
BP7		✖	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
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1		✖	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

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.5(TP53):c.532C>G (p.His1…	Pathogenic	Li-Fraumeni Syndrome	2024-08-05	2.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0	TP53
View	NM_000546.5(TP53):c.532C>G (p.His1…	Likely Pathogenic	Li-Fraumeni Syndrome	2020-01-24	1.0	-	TP53

Showing 1 to 2 of 2 rows

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