

Variant: NM_000546.5(TP53):c.517G>A (p.Val173Met)

Version: 1.1

CA10577579 [↗](#)

233951 (ClinVar) [↗](#)

Gene: TP53 ([HGNC:7157](#))
Condition: Li-Fraumeni syndrome ([MONDO:0018875](#))
Inheritance Mode: Autosomal dominant inheritance
UUID: 29aaaaea7-f2a2-441a-911c-111485dd6b50
Approved on: 2024/8/5
Published on: 2024/8/5

HGVS expressions

NM_000546.5:c.517G>A
NM_000546.5(TP53):c.517G>A (p.Val173Met)
NC_000017.11:g.7675095C>T
CM000679.2:g.7675095C>T
NC_000017.10:g.7578413C>T
CM000679.1:g.7578413C>T
NC_000017.9:g.7519138C>T
NG_017013.2:g.17456G>A
ENST00000503591.2:c.517G>A
ENST00000508793.6:c.517G>A
ENST00000509690.6:c.121G>A
ENST00000514944.6:c.238G>A
ENST00000604348.6:c.496G>A
ENST00000269305.9:c.517G>A
ENST00000269305.8:c.517G>A
ENST00000359597.8:c.517G>A
ENST00000413465.6:c.517G>A
ENST00000420246.6:c.517G>A
ENST00000445888.6:c.517G>A
ENST00000455263.6:c.517G>A
ENST00000504290.5:c.121G>A
ENST00000504937.5:c.121G>A
ENST00000505014.5:n.773G>A
ENST00000509690.5:c.121G>A
ENST00000510385.5:c.121G>A
ENST00000514944.5:c.238G>A
ENST00000574684.1:n.25G>A
ENST00000610292.4:c.400G>A
ENST00000610538.4:c.400G>A
ENST00000610623.4:c.40G>A
ENST00000615910.4:c.484G>A
ENST00000617185.4:c.517G>A
ENST00000618944.4:c.40G>A
ENST00000619186.4:c.40G>A
ENST00000619485.4:c.400G>A
ENST00000620739.4:c.400G>A
ENST00000622645.4:c.400G>A

	ENST000000635293.1:c.400G>A
	NM_001126112.2:c.517G>A
	NM_001126113.2:c.517G>A
	NM_001126114.2:c.517G>A
	NM_001126115.1:c.121G>A
	NM_001126116.1:c.121G>A
	NM_001126117.1:c.121G>A
	NM_001126118.1:c.400G>A
	NM_001276695.1:c.400G>A
	NM_001276696.1:c.400G>A
	NM_001276697.1:c.40G>A
	NM_001276698.1:c.40G>A
	NM_001276699.1:c.40G>A
	NM_001276760.1:c.400G>A
	NM_001276761.1:c.400G>A
	NM_001276695.2:c.400G>A
	NM_001276696.2:c.400G>A
	NM_001276697.2:c.40G>A
	NM_001276698.2:c.40G>A
	NM_001276699.2:c.40G>A
	NM_001276760.2:c.400G>A
	NM_001276761.2:c.400G>A
	NM_000546.6:c.517G>A
	NM_001126112.3:c.517G>A
	NM_001126113.3:c.517G>A
	NM_001126114.3:c.517G>A
	NM_001126115.2:c.121G>A
	NM_001126116.2:c.121G>A
	NM_001126117.2:c.121G>A
	NM_001126118.2:c.400G>A
	NM_001276695.3:c.400G>A
	NM_001276696.3:c.400G>A
	NM_001276697.3:c.40G>A
	NM_001276698.3:c.40G>A
	NM_001276699.3:c.40G>A
	NM_001276760.3:c.400G>A
	NM_001276761.3:c.400G>A

Pathogenic

Met criteria codes 5

PM1 PS3 PS4_Supporting
PM2_Supporting PP4_Moderate

Not Met criteria codes 12

PM5 PS1 PS2 BA1 PVS1
PP1 PP3 BS1 BS4 BS3 BS2
BP4

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.517G>A variant in TP53 is a missense variant predicted to cause substitution of valine by methionine at amino acid 173 (p.Val173Met). This variant has been reported in a proband meeting Classic 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; PMID16494995). 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, SCV000278424.6). This variant has an allele frequency of 0.000001695 (2/1180054 alleles) in the European (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). This variant has 27 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 (PM1, ≥ 10 somatic occurrences, PMID: 30311369). In vitro assays performed in yeast and 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). 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: PS4_Supporting, PP4_Moderate, PM2_Supporting, PM1, PS3. (Bayesian Points: 10; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

PM1			This variant has 27 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 (PM1; ≥ 10 somatic occurrences, PMID: 30311369).
PS3			In vitro assays performed in yeast and 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).
PS4_Supporting			This variant has been reported in a proband meeting Classic criteria. Based on this evidence, this variant scores 1 total points meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMID16494995).
PM2_Supporting			This variant has an allele frequency of 0.000001695 (2/1180054 alleles) in the European (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
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, SCV000278424.6).

Not Met criteria codes

PM5			4 different missense variants (p.Val173Leu, p.Val173Glu, p.Val173Ala, p.Val173Gly) in the same codon have been reported (ClinVar Variation IDs 1910599, 363548, 362896, 362895). 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).
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS2			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
PVS1			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).
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
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).

Curation History 



▼

▼

Showing 1 to 2 of 2 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.