

Variant: NM_000546.6(TP53):c.589G>A (p.Val197Met)

Version: 1.0

CA000285 [↗](#)

188060 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 71db6d7d-97cf-48a7-9d09-d4b48fdbbc5d

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HGVS expressions

NM_000546.6(TP53):c.589G>A (p.Val197Met)

NM_000546.6:c.589G>A

NC_000017.11:g.7674942C>T

CM000679.2:g.7674942C>T

NC_000017.10:g.7578260C>T

CM000679.1:g.7578260C>T

NC_000017.9:g.7518985C>T

NG_017013.2:g.17609G>A

ENST00000503591.2:c.589G>A

ENST00000508793.6:c.589G>A

ENST00000509690.6:c.193G>A

ENST00000514944.6:c.310G>A

ENST00000604348.6:c.568G>A

ENST00000269305.9:c.589G>A

ENST00000269305.8:c.589G>A

ENST00000359597.8:c.589G>A

ENST00000413465.6:c.589G>A

ENST00000420246.6:c.589G>A

ENST00000445888.6:c.589G>A

ENST00000455263.6:c.589G>A

ENST00000504290.5:c.193G>A

ENST00000504937.5:c.193G>A

ENST00000505014.5:n.845G>A

ENST00000509690.5:c.193G>A

ENST00000510385.5:c.193G>A

ENST00000514944.5:c.310G>A

ENST00000574684.1:n.67+111G>A

ENST00000610292.4:c.472G>A

ENST00000610538.4:c.472G>A

ENST00000610623.4:c.112G>A

ENST00000615910.4:c.556G>A

ENST00000617185.4:c.589G>A

ENST00000618944.4:c.112G>A

ENST00000619186.4:c.112G>A

ENST00000619485.4:c.472G>A

ENST00000620739.4:c.472G>A

ENST00000622645.4:c.472G>A

ENST00000635293.1:c.472G>A

NM_000546.5:c.589G>A

NM_001126112.2:c.589G>A

NM_001126113.2:c.589G>A

NM_001126114.2:c.589G>A

NM_001126115.1:c.193G>A

NM_001126116.1:c.193G>A

NM_001126117.1:c.193G>A

NM_001126118.1:c.472G>A

NM_001276695.1:c.472G>A

NM_001276696.1:c.472G>A

NM_001276697.1:c.112G>A

NM_001276698.1:c.112G>A

NM_001276699.1:c.112G>A

NM_001276760.1:c.472G>A

NM_001276761.1:c.472G>A

NM_001276695.2:c.472G>A

NM_001276696.2:c.472G>A

NM_001276697.2:c.112G>A

NM_001276698.2:c.112G>A

NM_001276699.2:c.112G>A

NM_001276760.2:c.472G>A

NM_001276761.2:c.472G>A

NM_001126112.3:c.589G>A

NM_001126113.3:c.589G>A

NM_001126114.3:c.589G>A

NM_001126115.2:c.193G>A

NM_001126116.2:c.193G>A

NM_001126117.2:c.193G>A

NM_001126118.2:c.472G>A

NM_001276695.3:c.472G>A

NM_001276696.3:c.472G>A

NM_001276697.3:c.112G>A

NM_001276698.3:c.112G>A

NM_001276699.3:c.112G>A

NM_001276760.3:c.472G>A

NM_001276761.3:c.472G>A

Likely Pathogenic

Met criteria codes 5

PS3_Moderate

PP4

PM1_Supporting

PM2_Supporting

PS4_Supporting

Not Met criteria codes 6

BA1

PS1

PP3

BS1

BS3

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 2.3.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

TP53 VCEP

The NM_000546.6:c.589G>A variant in TP53 is a missense variant predicted to cause substitution of valine by methionine at amino acid 197 (p.Val197Met). This variant has been reported in 1 family meeting Revised Chompret criteria and reported in 1 additional individual under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 1 total points meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; Internal contributors). At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, ClinVar SCV001186711.5, Internal lab contributors). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and loss of growth suppression activity, indicating that this variant impacts protein function (PS3_Moderate; PMIDs: 12826609, 30224644, 29979965). This variant has three 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). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Li-Fraumeni syndrome, based on the ACMG/AMP criteria applied as specified by the ClinGen TP53 VCEP: PS4_Supporting, PP4, PM2_Supporting, PS3_Moderate, PM1_Supporting (Bayesian Points: 6; VCEP specifications version 2.3).

Met criteria codes

PS3_Moderate			In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3_Moderate; PMIDs: 12826609, 30224644, 29979965).
PP4			At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, ClinVar SCV001186711.5, Internal lab contributors).
PM1_Supporting			This variant has 3 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 is absent from gnomAD v4.1.0 (PM2_Supporting).
PS4_Supporting			This variant has been reported in 1 family meeting Revised Chompret criteria and reported in 1 additional individual under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 1 total points meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; Internal contributors).

Not Met criteria codes

BA1			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
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, 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
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, 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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