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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
Approved on: 2025/12/5
Published on: 2025/12/5

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
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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
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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

PP4 PM2_Supporting PS3_Moderate PM1_Supporting PS4_Supporting

Not Met criteria codes 6

PS1 PP3 BA1 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**

Evidence submitted by expert panel

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

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

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).
BA1	✖	

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
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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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.6(TP53):c.589G>A (p.Val1...	Likely Pathogenic	Li-Fraumeni Syndrome	2025-12-05	1.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.3.0	TP53

Showing 1 to 1 of 1 rows

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