Variant: NM_000546.6(TP53):c.587G>A (p.Arg196Gln)

Version: 1.0

CA336434

216467 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 28a732f1-4606-40b6-b080-8b134000b282
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HGVS expressions

NM_000546.6:c.587G>A
NM_000546.6(TP53):c.587G>A (p.Arg196Gln)
NC_000017.11:g.7674944C>T
CM000679.2:g.7674944C>T
NC_000017.10:g.7578262C>T
CM000679.1:g.7578262C>T
NC_000017.9:g.7518987C>T
NG_017013.2:g.17607G>A
ENST00000503591.2:c.587G>A
ENST00000508793.6:c.587G>A
ENST00000509690.6:c.191G>A
ENST00000514944.6:c.308G>A
ENST00000604348.6:c.566G>A
ENST00000269305.9:c.587G>A
ENST00000269305.8:c.587G>A
ENST00000359597.8:c.587G>A
ENST00000413465.6:c.587G>A
ENST00000420246.6:c.587G>A
ENST00000445888.6:c.587G>A
ENST00000455263.6:c.587G>A
ENST00000504290.5:c.191G>A
ENST00000504937.5:c.191G>A
ENST00000505014.5:n.843G>A
ENST00000509690.5:c.191G>A
ENST00000510385.5:c.191G>A
ENST00000514944.5:c.308G>A
ENST00000574684.1:n.67+109G>A
ENST00000610292.4:c.470G>A
ENST00000610538.4:c.470G>A
ENST00000610623.4:c.110G>A
ENST00000615910.4:c.554G>A
ENST00000617185.4:c.587G>A
ENST00000618944.4:c.110G>A
ENST00000619186.4:c.110G>A
ENST00000619485.4:c.470G>A
ENST00000620739.4:c.470G>A
ENST00000622645.4:c.470G>A

ENST00000635293.1:c.470G>A
NM_000546.5:c.587G>A
NM_001126112.2:c.587G>A
NM_001126113.2:c.587G>A
NM_001126114.2:c.587G>A
NM_001126115.1:c.191G>A
NM_001126116.1:c.191G>A
NM_001126117.1:c.191G>A
NM_001126118.1:c.470G>A
NM_001276695.1:c.470G>A
NM_001276696.1:c.470G>A
NM_001276697.1:c.110G>A
NM_001276698.1:c.110G>A
NM_001276699.1:c.110G>A
NM_001276760.1:c.470G>A
NM_001276761.1:c.470G>A
NM_001276695.2:c.470G>A
NM_001276696.2:c.470G>A
NM_001276697.2:c.110G>A
NM_001276698.2:c.110G>A
NM_001276699.2:c.110G>A
NM_001276760.2:c.470G>A
NM_001276761.2:c.470G>A
NM_001126112.3:c.587G>A
NM_001126113.3:c.587G>A
NM_001126114.3:c.587G>A
NM_001126115.2:c.191G>A
NM_001126116.2:c.191G>A
NM_001126117.2:c.191G>A
NM_001126118.2:c.470G>A
NM_001276695.3:c.470G>A
NM_001276696.3:c.470G>A
NM_001276697.3:c.110G>A
NM_001276698.3:c.110G>A
NM_001276699.3:c.110G>A
NM_001276760.3:c.470G>A
NM_001276761.3:c.470G>A

Uncertain Significance

Met criteria codes 6

PP4_Moderate PP3 PS4_Supporting PM2_Supporting BS3_Supporting BS2

Not Met criteria codes 9

PS1 PS3 PP1 PM1 PM5 BA1 BS1 BS4 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.587G>A variant in TP53 is a missense variant predicted to cause substitution of arginine by glutamine at amino acid 196 (p.Arg196Gln). This variant has been reported in 2 unrelated probands meeting Revised Chompret 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; PMIDs: 30607672, Internal lab contributors). 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, Internal lab contributors). This variant has been observed in 4-7 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Moderate; Internal lab contributors). This variant has an allele frequency of 0.00001053 (17/1614074alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has a subpopulation allele frequency of <0.00004 in all non-bottleneck populations with 2 or more alleles present (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed retained growth suppression activity indicating that this variant does not impact protein function (BS3_Supporting; PMIDs: 29979965, 30224644). Computational predictor scores (BayesDel = 0.5787; Align GVGD = Class 35) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3). In summary, this variant meets the criteria to be classified as Uncertain Significance for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS4_Supporting, PP4_Moderate, BS2_Moderate, PM2_Supporting, BS3_Supporting, PP3. (Bayesian Points: 2; VCEP specifications version 2.3)

Met criteria codes

PP4_Moderate	ℹ	✓	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, Internal lab contributors).
PP3	ℹ	✓	Computational predictor scores (BayesDel = 0.5787; Align GVGD = Class 35) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3).
PS4_Supporting	ℹ	✓	This variant has been reported in 2 unrelated probands meeting Revised Chompret 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; PMIDs: 30607672, Internal lab contributors).
PM2_Supporting	ℹ	✓	This variant has an allele frequency of 0.00001053 (17/1614074alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has a subpopulation allele frequency of <0.00004 in all non-bottleneck populations with 2 or more alleles present (PM2_Supporting).
BS3_Supporting	ℹ	✓	In vitro assays performed in yeast and/or human cell lines showed retained growth suppression activity indicating that this variant does not impact protein function (BS3_Supporting; PMIDs: 29979965, 30224644). Kato (PMID: 12826609): partially functional Giacomelli (PMID: 30224644): no LOF Kotler (PMID: 29979965): noLOF.
BS2	ℹ	✓	MODERATE: This variant has been observed in 4-7 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Moderate; Internal lab contributors).

Not Met criteria codes

PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	ℹ	✖	This variant does not reside within a region of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PM1 not met).
PM5	ℹ	✖	3 different missense variants (c.587G>T, p.Arg196Leu; c.587G>C, p.Arg196Pro; c.586C>G, p.Arg196Gly) in the same codon have been reported (ClinVar Variation IDs: 100814, 231165, 232344). However, the variants are not eligible for PM5 consideration due to Grantham score (PM5 not evaluated).
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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