

Variant: NM_000546.5(TP53):c.467G>A (p.Arg156His)

Version: 1.1

CA000216 [↗](#)

127811 (ClinVar) [↗](#)

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

Condition: Li-Fraumeni syndrome 1 ([MONDO:0007903](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: ce57ae2b-139d-4e58-9f34-2bc237a4b09b

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HGVS expressions

NM_000546.5(TP53):c.467G>A (p.Arg156His)

NM_000546.5:c.467G>A

NC_000017.11:g.7675145C>T

CM000679.2:g.7675145C>T

NC_000017.10:g.7578463C>T

CM000679.1:g.7578463C>T

NC_000017.9:g.7519188C>T

NG_017013.2:g.17406G>A

ENST00000503591.2:c.467G>A

ENST00000508793.6:c.467G>A

ENST00000509690.6:c.71G>A

ENST00000514944.6:c.188G>A

ENST00000604348.6:c.446G>A

ENST00000269305.9:c.467G>A

ENST00000269305.8:c.467G>A

ENST00000359597.8:c.467G>A

ENST00000413465.6:c.467G>A

ENST00000420246.6:c.467G>A

ENST00000445888.6:c.467G>A

ENST00000455263.6:c.467G>A

ENST00000504290.5:c.71G>A

ENST00000504937.5:c.71G>A

ENST00000505014.5:n.723G>A

ENST00000508793.5:c.467G>A

ENST00000509690.5:c.71G>A

ENST00000510385.5:c.71G>A

ENST00000514944.5:c.188G>A

ENST00000610292.4:c.350G>A

ENST00000610538.4:c.350G>A

ENST00000610623.4:c.-11G>A

ENST00000615910.4:c.434G>A

ENST00000617185.4:c.467G>A

ENST00000618944.4:c.-11G>A

ENST00000619186.4:c.-11G>A

ENST00000619485.4:c.350G>A

ENST00000620739.4:c.350G>A

ENST00000622645.4:c.350G>A

	ENST00000635293.1:c.350G>A NM_001126112.2:c.467G>A NM_001126113.2:c.467G>A NM_001126114.2:c.467G>A NM_001126115.1:c.71G>A NM_001126116.1:c.71G>A NM_001126117.1:c.71G>A NM_001126118.1:c.350G>A NM_001276695.1:c.350G>A NM_001276696.1:c.350G>A NM_001276697.1:c.-11G>A NM_001276698.1:c.-11G>A NM_001276699.1:c.-11G>A NM_001276760.1:c.350G>A NM_001276761.1:c.350G>A NM_001276695.2:c.350G>A NM_001276696.2:c.350G>A NM_001276697.2:c.-11G>A NM_001276698.2:c.-11G>A NM_001276699.2:c.-11G>A NM_001276760.2:c.350G>A NM_001276761.2:c.350G>A NM_000546.6:c.467G>A NM_001126112.3:c.467G>A NM_001126113.3:c.467G>A NM_001126114.3:c.467G>A NM_001126115.2:c.71G>A NM_001126116.2:c.71G>A NM_001126117.2:c.71G>A NM_001126118.2:c.350G>A NM_001276695.3:c.350G>A NM_001276696.3:c.350G>A NM_001276697.3:c.-11G>A NM_001276698.3:c.-11G>A NM_001276699.3:c.-11G>A NM_001276760.3:c.350G>A NM_001276761.3:c.350G>A
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Uncertain Significance

Met criteria codes 3

- BS3_Supporting
- BS2_Supporting
- PS4_Moderate

Not Met criteria codes 14

- BS1
- BS4
- BP4
- BP2
- PS1
- PS2
- PS3
- BA1
- PP1
- PP3
- PM6
- PM2
- PM1
- PM5

Evidence Links 0

Expert Panel

TP53 VCEP 

Criteria Specification Information

 Criteria Specifications for this VCEP

TP53 VCEP

This variant has been reported in 4 probands meeting Revised Chompret criteria (PS4_Supporting; Internal laboratory and clinical contributors, SCV000186315.7). This variant has been observed in 4 60+ year old females without a cancer diagnosis (BS2_Supporting; internal laboratory contributor, SCV000186315.7). Transactivation assays show a partially functional variant according to Kato, et al. and there is no evidence of a dominant negative effect or loss of function according to Giacomelli, et al. (BS3_Supporting; PMID: 12826609, 30224644). In summary, the clinical significance of TP53 c.467G>A (p.Arg156His) is uncertain for Li-Fraumeni syndrome. ACMG/AMP criteria applied, as specified by the TP53 Variant Curation Expert Panel: PS4_moderate; BS2_supporting; BS4_supporting.

Met criteria codes

BS3_Supporting			Arg156His is partially functional in Kato data (52.65%). Giacomelli et al data shows p53WTNutlin3 Z-score is 0.85 (with cut off for dominant negative activity >=0.61) but the etoposide LOF Z-score is 0.178 (with <= -0.21as the cut off for loss of function). Kotler et al data is -2.72 (no LOF). Combined, this constitutes a BS3_Supporting evidence code.
BS2_Supporting			R156H is observed 1x in the FLOSSIES database, 4 cancer free 60+ from Ambry laboratories. 9 "potential" cancer free 60+ from Invitae, but could not be confirmed.
PS4_Moderate			Proband counting: Total = 2pts. Chompret to count as 0.5 and 1 for LFS. PMID:30709875 (not counted, fails to meet Chompret because cancers of relatives are unknown. Subject has pleomorphic sarcoma and treatment-AML, sister died 3yr unknown cancer, father died 42yr unknown cancer). PMID: 10435620. Not counted due to two variants. Subject and maternal lineage with two variants on one allele (R267Q and R156H) are LFS. PMID:28477317: not counted. Subject has fibrolamellar hepatocellular carcinoma at 14yr and a first cousin with osteosarcoma at age 10. PMID: 30092803: not counted, male with ileocecal valve adenocarcinoma at age 36 no family history available.; IARC family Ee100 (unpublished, in IARC): not counted. Female with breast cancer age 38 and first degree relative with sarcoma age 57. IARC family HEY10 PMID: 21059199 not counted 32 yr old with invasive ductal carcinoma. Authors note a family history of Li-Fraumeni Syndrome but it is not further detailed. Ambry laboratory had two cases that met Revised Chompret = 1 point. Internal clinical contributor had 2 cases that met Revised Chompret = 1 point.

Not Met criteria codes

BS1			10/28/19 variant is 0.00002 (4/251268) in Gnomad. All 4 alleles are in European (non-Finnish). It fails to meet the BS1 criteria of >0.0003 but <0.001 minor allele frequency, and does not have a minimum of 5 alleles in any one population.
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			Variant is Class C0 in align-GVGD (>C15 is considered pathogenic) and 0.1907 in BayesDel (>=0.16 is considered pathogenic). As these are not in concordance, the code cannot be applied.
BP2			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
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			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
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			Variant is Class C0 in align-GVGD (>C15 is considered pathogenic) and 0.1907 in BayesDel (>=0.16 is considered pathogenic). As these are not in concordance, the code cannot be applied.
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2			10/28/19 variant is 0.00002 (4/251268) in Gnomad. All 4 alleles are in European (non-Finnish). It fails to meet the BS1 criteria of >0.0003 but <0.001 minor allele frequency, and does not have a minimum of 5 alleles in any one population.
PM1			It is not a known hotspot and has no entry in the somatic hotspot database (cancerhotspots.org)
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 	
   	
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