

Variant: *NM_000038.6(APC):c.295C>T (p.Arg99Trp)*

Version: 1.0

CA007948 [↗](#)

135695 (ClinVar) [↗](#)

Gene: APC ([HGNC:324](#))

Condition: familial adenomatous polyposis 1 ([MONDO:0021056](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 6e18394e-9b0b-45fb-8586-e6fa585186a5

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HGVS expressions

NM_000038.6(APC):c.295C>T (p.Arg99Trp)

NM_000038.6:c.295C>T

NC_000005.10:g.112767263C>T

CM000667.2:g.112767263C>T

NC_000005.9:g.112102960C>T

CM000667.1:g.112102960C>T

NC_000005.8:g.112130859C>T

NG_008481.4:g.79743C>T

ENST00000502371.3:c.295C>T

ENST00000504915.3:c.295C>T

ENST00000505084.2:n.351C>T

ENST00000505350.2:c.*301C>T

ENST00000507379.6:c.325C>T

ENST00000509732.6:c.295C>T

ENST00000512211.7:c.295C>T

ENST00000257430.9:c.295C>T

ENST00000257430.8:c.295C>T

ENST00000507379.5:c.325C>T

ENST00000508376.6:c.295C>T

ENST00000508624.5:c.295C>T

ENST00000509732.5:c.295C>T

ENST00000512211.6:c.295C>T

NM_000038.5:c.295C>T

NM_001127510.2:c.295C>T

NM_001127511.2:c.325C>T

NM_001354895.1:c.295C>T

NM_001354896.1:c.295C>T

NM_001354897.1:c.325C>T

NM_001354898.1:c.220C>T

NM_001354899.1:c.295C>T

NM_001354900.1:c.118C>T

NM_001354901.1:c.118C>T

NM_001354902.1:c.325C>T

NM_001354903.1:c.295C>T

NM_001354904.1:c.220C>T

NM_001354905.1:c.118C>T

NM_001354906.1:c.-741C>T

NM_001127510.3:c.295C>T
NM_001127511.3:c.325C>T
NM_001354895.2:c.295C>T
NM_001354896.2:c.295C>T
NM_001354897.2:c.325C>T
NM_001354898.2:c.220C>T
NM_001354899.2:c.295C>T
NM_001354900.2:c.118C>T
NM_001354901.2:c.118C>T
NM_001354902.2:c.325C>T
NM_001354903.2:c.295C>T
NM_001354904.2:c.220C>T
NM_001354905.2:c.118C>T
NM_001354906.2:c.-741C>T

Benign

Met criteria codes 5

BP5 BP1 BP2 BS1 BS2

Not Met criteria codes 13

BP7 BS4 BS3 PP1 PP4
PM1 PM5 PM6 PS1 PS2
PS3 PS4 PVS1

Evidence Links 0

Expert Panel

InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP

The c.295C>T variant in APC is a missense variant predicted to cause substitution of Arginine by Tryptophan at amino acid position 99 (p.Arg99Trp). APC is defined by the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel (HCCP VCEP) as a gene for which primarily truncating variants are known to cause disease (BP1). The highest population minor allele frequency of the variant c.295C>T in gnomAD v2.1.1 (non-cancer) is 0.0007355 (95/129170 alleles) in the European (non-Finnish) population, which is higher than the HCCP VCEP threshold ($\geq 0.001\%$) for BS1 (BS1). This variant has been observed in heterozygous state in more than 1000 healthy unrelated adult individuals worth ≥ 10 healthy individual points in total (BS2; Invitae and Ambry Genetics internal data). It has also been observed once in a homozygous state (Ambry Genetics internal data). This variant has been observed 4 times with other APC variants deemed (likely) pathogenic by the HCCP VCEP in individuals with FAP (BP2; PMIDs 23159591, 25604157, Bonn internal data). Finally, this variant has been observed in 6 patients with an alternate molecular basis for disease (BP5; Leiden University Medical Center internal data). In summary, this variant meets the criteria to be classified as Benign for FAP based on the ACMG/AMP criteria applied, as specified by the HCCP VCEP: BS1, BS2, BP1, BP2 (VCEP specifications version 1; date of approval 12/12/2022).

Met criteria codes

BP5



This variant has been observed in 6 patient(s) with an alternate molecular basis for disease – co-occurrences observed with pathogenic variants in CHEK2, ATM, MSH6, BRCA1, MLH1, PTEN (BP5; Leiden University Medical Center internal data).

BP1



APC is defined by the InSiGHT ClinGen Hereditary Colorectal Cancer/Polypsis Variant Curation Expert Panel (HCCP VCEP) as a gene for which primarily truncating variants are known to cause disease (BP1).

BP2			This variant has been observed in trans with the LoF variants (p.Ser1222Ter and large deletion of exon 15, respectively) in individuals with FAP (PMID: 23159591). Moreover, the variant was detected together with a LoF variant (c.1972_1975del;p.Glu658Thrfs*11) in a proband with multiple colorectal polyps, phase unknown (PMID: 25604157). Finally, This variant has been observed in an unknown phase with the variant c.646C>T, p. p.Arg216Ter (Bonn internal data) which is classified as Pathogenic by the InSiGHT ClinGen Hereditary Colorectal Cancer/ Polypsis Variant Curation Expert Panel in an individual with FAP.
BS1			The highest population minor allele frequency of the variant c.295C>T in gnomAD v2.1.1 (non-cancer) is 0.0007355 (95/129170 alleles) in European (non-Finnish) population, which is higher than the InSiGHT ClinGen Hereditary Colorectal Cancer/Polypsis VCEP threshold ($\geq 0.001\%$) for BS1, and therefore meets this criterion (BS1).
BS2			This variant has been observed in heterozygous state in more than 1000 healthy unrelated adult individuals worth ≥ 10 healthy individual points in total (BS2; Invitae internal data, Ambry Genetics internal data). It has also been observed once in homozygous state (Ambry Genetics internal data).

Not Met criteria codes

BP7			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
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			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
PS4			This variant has been reported in 29 patients, with 1 proband meeting phenotypic criteria, resulting in a total phenotype score of 0.5 points (PS4_variable not met, PMID11606402, GeneDX internal data, Leiden University Medical Centre internal data, Peter MacCallum Cancer Centre internal data, Bonn internal data, PMID11606402).
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History



 

 

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