

Variant: *NM_000038.6(APC):c.1042C>T (p.Arg348Ter)*

Version: 1.1

CA16021325 [↗](#)

955439 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 011221f1-ca1b-4750-9435-03f4f4380288

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HGVS expressions

NM_000038.6(APC):c.1042C>T (p.Arg348Ter)

NM_000038.6:c.1042C>T

NC_000005.10:g.112819074C>T

CM000667.2:g.112819074C>T

NC_000005.9:g.112154771C>T

CM000667.1:g.112154771C>T

NC_000005.8:g.112182670C>T

NG_008481.4:g.131554C>T

ENST00000502371.3:c.1042C>T

ENST00000504915.3:c.1042C>T

ENST00000505084.2:n.1098C>T

ENST00000505350.2:c.*1048C>T

ENST00000507379.6:c.988C>T

ENST00000509732.6:c.1042C>T

ENST00000512211.7:c.1042C>T

ENST00000257430.9:c.1042C>T

ENST00000257430.8:c.1042C>T

ENST00000507379.5:c.988C>T

ENST00000508376.6:c.1042C>T

ENST00000508624.5:c.*364C>T

ENST00000512211.6:c.1042C>T

NM_000038.5:c.1042C>T

NM_001127510.2:c.1042C>T

NM_001127511.2:c.988C>T

NM_001354895.1:c.1042C>T

NM_001354896.1:c.1042C>T

NM_001354897.1:c.1072C>T

NM_001354898.1:c.967C>T

NM_001354899.1:c.958C>T

NM_001354900.1:c.865C>T

NM_001354901.1:c.865C>T

NM_001354902.1:c.964-195C>T

NM_001354903.1:c.934-195C>T

NM_001354904.1:c.859-195C>T

NM_001354905.1:c.757-195C>T

NM_001354906.1:c.193C>T

NM_001127510.3:c.1042C>T

NM_001127511.3:c.988C>T
NM_001354895.2:c.1042C>T
NM_001354896.2:c.1042C>T
NM_001354897.2:c.1072C>T
NM_001354898.2:c.967C>T
NM_001354899.2:c.958C>T
NM_001354900.2:c.865C>T
NM_001354901.2:c.865C>T
NM_001354902.2:c.964-195C>T
NM_001354903.2:c.934-195C>T
NM_001354904.2:c.859-195C>T
NM_001354905.2:c.757-195C>T
NM_001354906.2:c.193C>T

Uncertain Significance

Met criteria codes 3

BS2_Supporting

PM2_Supporting

PS4_Supporting

Not Met criteria codes 1

PVS1

Evidence Links 0

Expert Panel

InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP

Criteria Specification Information

Criteria Specification: ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for APC Version 2.1.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP

The NM_000038.6(APC):c.1042C>T variant in APC is predicted to cause a premature stop codon (p.R348Ter) located between codon 49 and 2645 in biologically relevant exon 10 (coding exon 9) in a gene in which loss-of-function is an established disease mechanism. However, based on unpublished RNA analyses from Ambry Genetics, the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP (HCCP VCEP) does not consider this variant to be applicable to PVS1. The RNA analyses showed that this variant results in an in-frame aberrant transcript lacking part of exon 10 [r.934_1074del (p.V312_Q358del)]. In addition, an increased expression of a naturally occurring alternative transcript (r.934_1236del (p.V312_Q412del), known as “exon 9a”) was observed relative to controls. The predicted premature stop codon (p.R348Ter) was excluded from both the aberrant and naturally occurring transcripts and might provide a rescue mechanism for this nonsense alteration. The total minor allele frequency in gnomAD v2.1.1 (non-cancer) is 0.000004 (1/251004 alleles), which is lower than the HCCP VCEP threshold 0.00001 for PM2_Supporting if the allele count is ≤ 1 and therefore meets this criterion (PM2_Supporting). This variant has been reported in three families with a polyposis phenotype, resulting in a total phenotype score of 1.5 points (PS4_Supporting, [PMID: 11754114 and 12007223; CanVIG-UK]). On the other hand, this variant has been observed in heterozygous state in 7 healthy unrelated adult individuals worth ≥ 6 healthy individual points in total (BS2_Supporting; [Ambry Genetics, Invitae, UK Biobank, 100,000 Genomes Project]). Due to conflicting evidence, this variant is classified as a variant of uncertain significance (VUS) for autosomal-dominant inherited FAP based on the ACMG/AMP criteria applied, as specified by the HCCP VCEP: criteria PS4_Supporting, PM2_Supporting and BS2_Supporting applied (VCEP specifications version 2.0.3; date of approval 7/24/2023).

Met criteria codes

BS2_Supporting			This variant has been observed in heterozygous state in 7 healthy unrelated adult individuals worth ≥ 6 healthy individual points in total (BS2_Supporting; [Ambry Genetics, Invitae, UK Biobank, 100,000 Genomes Project]).
PM2_Supporting			The total minor allele frequency in gnomAD v2.1.1 (non-cancer) is 0.000004 (1/251004 alleles), which is lower than the HCCP VCEP threshold 0.00001 for PM2_Supporting if the allele count is ≤ 1 and therefore meets this criterion (PM2_Supporting).
PS4_Supporting			This variant has been reported in three families with a polyposis phenotype, resulting in a total phenotype score of 1.5 points (PS4_Supporting, [PMID: 11754114 and 12007223; CanVIG-UK]).
Not Met criteria codes			
PVS1			The NM_000038.6(APC):c.1042C>T variant in APC is predicted to cause a premature stop codon (p.R348Ter) located between codon 49 and 2645 in biologically relevant exon 10 (coding exon 9) in a gene in which loss-of-function is an established disease mechanism. However, based on unpublished RNA analyses from Ambry Genetics, the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP (HCCP VCEP) does not consider this variant to be applicable to PVS1. The RNA analyses showed that this variant results in an in-frame aberrant transcript lacking part of exon 10 [r.934_1074del (p.V312_Q358del)]. In addition, an increased expression of a naturally occurring alternative transcript (r.934_1236del (p.V312_Q412del), known as “exon 9a”) was observed relative to controls. The predicted premature stop codon (p.R348Ter) was excluded from both the aberrant and naturally occurring transcripts and might provide a rescue mechanism for this nonsense alteration.

Curation History 			
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