

Variant: NM_000038.6(APC):c.1458T>C (p.Tyr486=)

Version: 1.0

CA005169 [↗](#)

42238 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: ceaf12ac-7838-446c-ae16-b4059d1b3f42

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HGVS expressions

NM_000038.6(APC):c.1458T>C (p.Tyr486=)

NM_000038.6:c.1458T>C

NC_000005.10:g.112827157T>C

CM000667.2:g.112827157T>C

NC_000005.9:g.112162854T>C

CM000667.1:g.112162854T>C

NC_000005.8:g.112190753T>C

NG_008481.4:g.139637T>C

ENST00000502371.3:c.1408+5166T>C

ENST00000504915.3:c.1512T>C

ENST00000505084.2:n.1514T>C

ENST00000505350.2:c.*1464T>C

ENST00000507379.6:c.1404T>C

ENST00000509732.6:c.1458T>C

ENST00000512211.7:c.1458T>C

ENST00000257430.9:c.1458T>C

ENST00000257430.8:c.1458T>C

ENST00000502371.2:c.96+5166T>C

ENST00000504915.2:c.147T>C

ENST00000507379.5:c.1404T>C

ENST00000508376.6:c.1458T>C

ENST00000508624.5:c.*780T>C

ENST00000512211.6:c.1458T>C

NM_000038.5:c.1458T>C

NM_001127510.2:c.1458T>C

NM_001127511.2:c.1404T>C

NM_001354895.1:c.1458T>C

NM_001354896.1:c.1512T>C

NM_001354897.1:c.1488T>C

NM_001354898.1:c.1383T>C

NM_001354899.1:c.1374T>C

NM_001354900.1:c.1335T>C

NM_001354901.1:c.1281T>C

NM_001354902.1:c.1185T>C

NM_001354903.1:c.1155T>C

NM_001354904.1:c.1080T>C

NM_001354905.1:c.978T>C

NM_001354906.1:c.609T>C
NM_001127510.3:c.1458T>C
NM_001127511.3:c.1404T>C
NM_001354895.2:c.1458T>C
NM_001354896.2:c.1512T>C
NM_001354897.2:c.1488T>C
NM_001354898.2:c.1383T>C
NM_001354899.2:c.1374T>C
NM_001354900.2:c.1335T>C
NM_001354901.2:c.1281T>C
NM_001354902.2:c.1185T>C
NM_001354903.2:c.1155T>C
NM_001354904.2:c.1080T>C
NM_001354905.2:c.978T>C
NM_001354906.2:c.609T>C

Benign

Met criteria codes 3

BP7 BP4 BA1

Not Met criteria codes 2

PS3 PM2

Evidence Links 0

Expert Panel

InSiGHT Hereditary Colorectal Cancer/Polypsis VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

InSiGHT Hereditary Colorectal Cancer/Polypsis VCEP

The c.1458T>C (p.Tyr486=) variant in APC is a synonymous (silent) variant that is not predicted to impact splicing (BP4, BP7). The highest population minor allele frequency (non-cancer) in gnomAD v2.1.1 is 69.75% in Latino/Admixed American population, which is higher than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polypsis Variant Curation Expert Panel (HCCP VCEP) threshold ($\geq 0.1\%$) for BA1, and therefore meets this criterion (BA1). 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: BA1, BP4, BP7 (VCEP specifications Version 1.0, date of approval: 12/12/2022).

Met criteria codes

BP7			The c.1458T>C (p.Tyr486=) variant (NM_000038.6)) is a synonymous (silent) variant that is not predicted by SpliceAI and VarSeak to impact splicing (BP4, BP7).
BP4			The results from 2 in silico splicing predictors (SpliceAI and varSEAK) support that this variant does not affect splicing (BP4).
BA1			The highest population minor allele frequency (non-cancer) in gnomAD v2.1.1 is 69.75% in Latino/Admixed American population, which is higher than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polypsis threshold ($\geq 0.1\%$) for BA1, and therefore meets this criterion (BA1).

Not Met criteria codes

PS3	 	Bioinformatics prediction suggested that this variant was likely a disease-causing polymorphism and may have induced the exon skipping of APC (PMID: 30272267). Using mini-gene system transfected into HeLa cells, the PCR product from the mutant mini-gene was smaller than that from the wild-type, which suggested that the mini-gene system encoding mutant induced the skipping of exon 12 in APC. However, this result does not meet the requirement to apply PS3 or modified PS3.
PM2		No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History



Showing 1 to 1 of 1 rows

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