

Variant: *NM_000038.6(APC):c.422G>A (p.Arg141Lys)*

Version: 1.0

CA16022245 [↗](#)

824696 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 393b5f9f-c4b7-4db7-a443-11d099ae1c2a

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HGVS expressions

NM_000038.6(APC):c.422G>A (p.Arg141Lys)

NM_000038.6:c.422G>A

NC_000005.10:g.112767390G>A

CM000667.2:g.112767390G>A

NC_000005.9:g.112103087G>A

CM000667.1:g.112103087G>A

NC_000005.8:g.112130986G>A

NG_008481.4:g.79870G>A

ENST00000502371.3:c.422G>A

ENST00000504915.3:c.422G>A

ENST00000505084.2:n.478G>A

ENST00000505350.2:c.*428G>A

ENST00000507379.6:c.452G>A

ENST00000509732.6:c.422G>A

ENST00000512211.7:c.422G>A

ENST00000257430.9:c.422G>A

ENST00000257430.8:c.422G>A

ENST00000507379.5:c.452G>A

ENST00000508376.6:c.422G>A

ENST00000508624.5:c.422G>A

ENST00000512211.6:c.422G>A

NM_000038.5:c.422G>A

NM_001127510.2:c.422G>A

NM_001127511.2:c.452G>A

NM_001354895.1:c.422G>A

NM_001354896.1:c.422G>A

NM_001354897.1:c.452G>A

NM_001354898.1:c.347G>A

NM_001354899.1:c.422G>A

NM_001354900.1:c.245G>A

NM_001354901.1:c.245G>A

NM_001354902.1:c.452G>A

NM_001354903.1:c.422G>A

NM_001354904.1:c.347G>A

NM_001354905.1:c.245G>A

NM_001354906.1:c.-614G>A

NM_001127510.3:c.422G>A

NM_001127511.3:c.452G>A
NM_001354895.2:c.422G>A
NM_001354896.2:c.422G>A
NM_001354897.2:c.452G>A
NM_001354898.2:c.347G>A
NM_001354899.2:c.422G>A
NM_001354900.2:c.245G>A
NM_001354901.2:c.245G>A
NM_001354902.2:c.452G>A
NM_001354903.2:c.422G>A
NM_001354904.2:c.347G>A
NM_001354905.2:c.245G>A
NM_001354906.2:c.-614G>A

Uncertain Significance

Met criteria codes 2

PM2_Supporting PVS1_Strong

Not Met criteria codes 1

BS2

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.422G>A (p.Arg141Lys) variant in APC is a G to non-G change at the last nucleotide of exon 4. It is predicted to cause skipping of exon 4, resulting in a frameshift in a gene in which loss-of-function is an established disease mechanism (List B; PVS1_Strong). However, exon skipping could not be confirmed by RTPCRSeq data. Even though this could be based on technical limitations, the variant allele was present in 35% of normally spliced reads, so the splicing impact seems to be low (internal data Ambry Genetics). The total minor allele frequency in gnomAD v2.1.1 (non-cancer) is 0.0004% (1/236810 alleles), which is lower than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP (HCCP VCEP) threshold of < 0.001% (0.00001) for PM2_Supporting if the allele count is ≤ 1 and therefore meets this criterion (PM2_Supporting). The variant has been reported in three individuals without a colorectal cancer/polyposis associated phenotype (one person fulfills 0.5 points as a “healthy individual,” for the other two not enough information is available; BS2 not met; internal data Ambry Genetics). In summary, this variant is a variant of uncertain significance (VUS) for autosomal-dominant inherited FAP based on the ACMG/AMP criteria applied, as specified by the HCCP VCEP: PVS1_Strong and PM2_Supporting (VCEP specifications version v2.1.0; date of approval 11/24/2023).

Met criteria codes

PM2_Supporting  

The total minor allele frequency in gnomAD v2.1.1 (non-cancer) is 0.0004% (1/236810 alleles), which is lower than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP (HCCP VCEP) threshold of < 0.001% (0.00001) for PM2_Supporting if the allele count is ≤ 1 and therefore meets this criterion (PM2_Supporting).

PVS1_Strong			The NM_000038.6(APC):c.422G>A (p.Arg141Lys) variant in APC is a G to non-G change at the last nucleotide of exon 4. It is predicted to cause skipping of exon 4, resulting in a frameshift in a gene in which loss-of-function is an established disease mechanism (List B; PVS1_Strong). However, exon skipping could not be confirmed by RTPCRSeq data. Even though this could be based on technical limitations, the variant allele was present in 35% of normally spliced reads, so the splicing impact seems to be low (internal data Ambry Genetics).
Not Met criteria codes			
BS2			The variant has been reported in three individuals without a colorectal cancer/polypsis associated phenotype (one person fulfills 0.5 points as a “healthy individual,” for the other two not enough information is available; BS2 not met; internal data Ambry Genetics).

Curation History 			
    			
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