Variant: NM_000038.6(APC):c.423-4del

Version: 1.0

CA009327

181781 (ClinVar)

Gene: APC (HGNC:324)
Condition: familial adenomatous polyposis 1 (MONDO:0021056)
Inheritance Mode: Autosomal dominant inheritance
UUID: 29a46390-aaf6-4be6-b493-b5a954e33b74
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HGVS expressions

NM_000038.6:c.423-4del
NM_000038.6(APC):c.423-4del
NC_000005.10:g.112775625del
CM000667.2:g.112775625del
NC_000005.9:g.112111322del
CM000667.1:g.112111322del
NC_000005.8:g.112139221del
NG_008481.4:g.88105del
ENST00000502371.3:c.423-4del
ENST00000504915.3:c.423-4del
ENST00000505084.2:n.479-4del
ENST00000505350.2:c.*429-4del
ENST00000507379.6:c.453-4del
ENST00000509732.6:c.423-4del
ENST00000512211.7:c.423-4del
ENST00000257430.9:c.423-4del
ENST00000257430.8:c.423-4del
ENST00000507379.5:c.453-4del
ENST00000508376.6:c.423-4del
ENST00000508624.5:c.423-4del
ENST00000512211.6:c.423-4del
NM_000038.5:c.423-4del
NM_001127510.2:c.423-4del
NM_001127511.2:c.453-4del
NM_001354895.1:c.423-4del
NM_001354896.1:c.423-4del
NM_001354897.1:c.453-4del
NM_001354898.1:c.348-4del
NM_001354899.1:c.423-4del
NM_001354900.1:c.246-4del
NM_001354901.1:c.246-4del
NM_001354902.1:c.453-4del
NM_001354903.1:c.423-4del
NM_001354904.1:c.348-4del
NM_001354905.1:c.246-4del
NM_001354906.1:c.-613-4del
NM_001127510.3:c.423-4del

NM_001127511.3:c.453-4del
NM_001354895.2:c.423-4del
NM_001354896.2:c.423-4del
NM_001354897.2:c.453-4del
NM_001354898.2:c.348-4del
NM_001354899.2:c.423-4del
NM_001354900.2:c.246-4del
NM_001354901.2:c.246-4del
NM_001354902.2:c.453-4del
NM_001354903.2:c.423-4del
NM_001354904.2:c.348-4del
NM_001354905.2:c.246-4del
NM_001354906.2:c.-613-4del

Benign

Met criteria codes 3

BS3_Supporting BA1 BP4

Not Met criteria codes 9

BS1 PP2 PP3 PS1 PS3 PM5 PM2 PVS1 BP1

Evidence Links 1

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.423-4del variant in APC is an intronic variant which results in the deletion of adenine at position -4 of intron 4. The highest allele frequency is 5.48% in gnomAD v3.1.2, which is higher than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel (HCCP VCEP) threshold for BA1 (≥ 0.1%). RNA assays showed no splicing mutation, indicating that this variant does not impact protein function (BS3_Supporting; PMID22447671). Finally, the results from ≥2 in silico splicing predictors support that this variant does not affect splicing (BP4). 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, BS3_Supporting, BP4. (VCEP specifications version 1; date of approval: 12/12/2022).

Met criteria codes

BS3_Supporting	✔	RNA assays of an APC cDNA fragment spanning from exons 3 to 5 in patient subjects carrying the variant c.423-4del showed no splicing mutation at APC exons 3-5, indicating that this variant does not impact protein function (PMID22447671)(BS3_Supporting). After analyses of RNA and subsequent PCR amplification and sequence, no exon splices mutations were found at APC exons 3–5 (Supp. Fig. S1). PubMed:22447671
BA1	✔	The highest population minor allele frequency of the variant c.423-4del in gnomAD v3.1.2 is 0.05478 (2140/39064 alleles) in non-cancer African/African American population, which is higher than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis threshold threshold (≥ 0.1%) for BA1, and therefore meets this criterion (BA1).

BP4	✔	The results from ≥2 in silico splicing predictors (SpliceAI, MaxEntScan, VarSeak) support that this variant does not affect splicing (BP4).

Not Met criteria codes

BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	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
PS3	✖	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
PM2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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