Variant: NM_000038.6(APC):c.4420G>A (p.Ala1474Thr)

Version: 1.0

CA009532

133530 (ClinVar)

Gene: APC (HGNC:324)
Condition: familial adenomatous polyposis 1 (MONDO:0021056)
Inheritance Mode: Autosomal dominant inheritance
UUID: 84be63ca-6205-415b-8aa7-b32b28a56daf
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HGVS expressions

NM_000038.6:c.4420G>A
NM_000038.6(APC):c.4420G>A (p.Ala1474Thr)
NC_000005.10:g.112840014G>A
CM000667.2:g.112840014G>A
NC_000005.9:g.112175711G>A
CM000667.1:g.112175711G>A
NC_000005.8:g.112203610G>A
NG_008481.4:g.152494G>A
ENST00000504915.3:c.4474G>A
ENST00000505350.2:c.*4426G>A
ENST00000507379.6:c.4366G>A
ENST00000509732.6:c.4420G>A
ENST00000512211.7:c.4420G>A
ENST00000257430.9:c.4420G>A
ENST00000257430.8:c.4420G>A
ENST00000508376.6:c.4420G>A
ENST00000508624.5:c.*3742G>A
ENST00000520401.1:c.230+11042G>A
NM_000038.5:c.4420G>A
NM_001127510.2:c.4420G>A
NM_001127511.2:c.4366G>A
NM_001354895.1:c.4420G>A
NM_001354896.1:c.4474G>A
NM_001354897.1:c.4450G>A
NM_001354898.1:c.4345G>A
NM_001354899.1:c.4336G>A
NM_001354900.1:c.4297G>A
NM_001354901.1:c.4243G>A
NM_001354902.1:c.4147G>A
NM_001354903.1:c.4117G>A
NM_001354904.1:c.4042G>A
NM_001354905.1:c.3940G>A
NM_001354906.1:c.3571G>A
NM_001127510.3:c.4420G>A
NM_001127511.3:c.4366G>A
NM_001354895.2:c.4420G>A
NM_001354896.2:c.4474G>A

NM_001354897.2:c.4450G>A
NM_001354898.2:c.4345G>A
NM_001354899.2:c.4336G>A
NM_001354900.2:c.4297G>A
NM_001354901.2:c.4243G>A
NM_001354902.2:c.4147G>A
NM_001354903.2:c.4117G>A
NM_001354904.2:c.4042G>A
NM_001354905.2:c.3940G>A
NM_001354906.2:c.3571G>A

Benign

Met criteria codes 3

BA1 BS3_Supporting BP1

Not Met criteria codes 4

PP3 PM2 PS3 BP4

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.4420G>A variant in APC is a missense variant predicted to cause the substitution of Alanine by Threonine at amino acid position 1474 (p.Ala1474Thr). The highest population minor allele frequency of this variant in gnomAD v2.1.1 (non-cancer) is 1.13% in the African/African American population, which is higher than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Expert Panel's (HCCP VCEP) threshold (≥ 0.1%) for BA1, and therefore meets this criterion (BA1). Functional study of β-catenin-regulated transcription assays indicate that this alteration suppresses CRT as effectively as wild type (BS3_Supporting; PMID: 18199528). Finally, APC is defined by the HCCP VCEP as a gene for which primarily truncating variants are known to cause disease (BP1). 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, BP1, BS3_Supporting (VCEP specifications version 1; date of approval: 12/12/2022).

Met criteria codes

BA1	✔	The highest population minor allele frequency (non-cancer) in gnomAD v2.1.1 is 1.131% in the African/African American population, which is higher than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis threshold (≥ 0.1%) for BA1, and therefore meets this criterion (BA1).
BS3_Supporting	✔	Functional study of β-catenin-regulated transcription assays indicated that this alteration suppressed CRT as effectively as wild type (PubMed:18199528, BS3_Supporting).
BP1	✔	APC, in which the variant was identified, is defined by the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP as a gene for which primarily truncating variants are known to cause disease (BP1).

Not Met criteria codes

PP3	✖	Multiple lines of computational evidence suggest no splicing impact (SpliceAI and varSEAK).
PM2	✖	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
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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