

Variant: *NM_000038.6(APC):c.3084T>A (p.Ser1028Arg)*

Version: 1.0

CA10578350 [↗](#)

233215 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: f412a530-ecd2-4ceb-bd23-0b0081fee028

Approved on: 2023/2/25

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HGVS expressions

NM_000038.6:c.3084T>A

NM_000038.6(APC):c.3084T>A (p.Ser1028Arg)

NC_000005.10:g.112838678T>A

CM000667.2:g.112838678T>A

NC_000005.9:g.112174375T>A

CM000667.1:g.112174375T>A

NC_000005.8:g.112202274T>A

NG_008481.4:g.151158T>A

ENST00000502371.3:c.2749T>A

ENST00000504915.3:c.3138T>A

ENST00000505350.2:c.*3090T>A

ENST00000507379.6:c.3030T>A

ENST00000509732.6:c.3084T>A

ENST00000512211.7:c.3084T>A

ENST00000257430.9:c.3084T>A

ENST00000257430.8:c.3084T>A

ENST00000502371.2:c.1437T>A

ENST00000507379.5:c.3030T>A

ENST00000508376.6:c.3084T>A

ENST00000508624.5:c.*2406T>A

ENST00000512211.6:c.3084T>A

ENST00000520401.1:c.230+9706T>A

NM_000038.5:c.3084T>A

NM_001127510.2:c.3084T>A

NM_001127511.2:c.3030T>A

NM_001354895.1:c.3084T>A

NM_001354896.1:c.3138T>A

NM_001354897.1:c.3114T>A

NM_001354898.1:c.3009T>A

NM_001354899.1:c.3000T>A

NM_001354900.1:c.2961T>A

NM_001354901.1:c.2907T>A

NM_001354902.1:c.2811T>A

NM_001354903.1:c.2781T>A

NM_001354904.1:c.2706T>A

NM_001354905.1:c.2604T>A

NM_001354906.1:c.2235T>A

NM_001127510.3:c.3084T>A
NM_001127511.3:c.3030T>A
NM_001354895.2:c.3084T>A
NM_001354896.2:c.3138T>A
NM_001354897.2:c.3114T>A
NM_001354898.2:c.3009T>A
NM_001354899.2:c.3000T>A
NM_001354900.2:c.2961T>A
NM_001354901.2:c.2907T>A
NM_001354902.2:c.2811T>A
NM_001354903.2:c.2781T>A
NM_001354904.2:c.2706T>A
NM_001354905.2:c.2604T>A
NM_001354906.2:c.2235T>A

Likely Pathogenic

Met criteria codes 5

- PS3_Supporting
- PS4_Moderate
- PP1_Moderate
- PM2_Supporting
- PM5_Supporting

Not Met criteria codes 1

- PS1

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.3084T>A variant in APC is a missense variant predicted to cause the substitution of serine by arginine at amino acid position 1028 p. (Ser1028Arg). This variant has been reported in 6 probands meeting phenotypic criteria, resulting in a total phenotype score of 3 (PS4_Moderate; Ambry Genetics internal data). This variant has been reported to segregate with FAP in 3 meioses in 2 families (6 meioses in total) (PP1_Moderate; Ambry Genetics internal data). This variant is demonstrated to increased β -catenin regulated transcription activity and decreased binding to β -catenin by surface plasmon resonance (PS3_Supporting, Barcelona internal data). Another missense variant c.3083G>T (p.Ser1028Ile) in the same codon has been classified as Likely Pathogenic for FAP by the ClinGen InSiGHT Hereditary Colorectal Cancers/ Polyposis VCEP (PM5_Supporting). Finally, this variant is absent from gnomAD v2.1.1 (PM2_Supporting). In summary, this variant is classified as Likely Pathogenic for FAP based on the ACMG/AMP criteria applied, as specified by the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel: PS4_Moderate, PP1_Moderate, PS3_Supporting, PM2_Supporting, PM5_Supporting (VCEP Specification version 1; date of approval: 12/12/2022).

Met criteria codes

- | | | | |
|----------------|---|---|--|
| PS3_Supporting |  |  | PS3_Supporting (increased β -catenin regulated transcription activity and decreased binding to β -catenin by surface plasmon resonance, internal data). |
| PS4_Moderate |  |  | This variant has been reported in 6 probands meeting phenotypic criteria, resulting in a total phenotype score of 3 (PS4_Moderate, Ambry Genetics, Invitae internal data). |

PP1_Moderate			This variant has been reported to segregate with FAP in 3 meioses in 2 families (6 meiosis in total) (PP1_moderate; Ambry Internal data).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PM5_Supporting			Another missense variant c.3083G>T (p.Ser1028Ile) in the same codon has been classified as Likely Pathogenic for FAP by the ClinGen InSiGHT Hereditary Colorectal Cancers/ Polyposis VCEP.
Not Met criteria codes			
PS1			The amino acid change (p.Ser1028Arg) resulting from a different nucleotide change c.3084T>G has been classified as a variant of unknown significance for FAP according to the APC-VCEP evidence codes (internal data Ambry and Invitae) (PS1_variable not met).

Curation History 			
			
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