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# *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
**Published on**: 2023/3/14

## *HGVS expressions*

**NM_000038.6(APC):c.3084T>A (p.Ser1028Arg)**
**NM_000038.6:c.3084T>A**
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 PP1_Moderate PM2_Supporting PS4_Moderate 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 meiosis 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). |
| **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). |
| **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). |
| **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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