

Variant: *NM_000038.6(APC):c.1902T>G (p.Ser634Arg)*

Version: 1.0

CA10578330 [↗](#)

231954 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 9ed4d6b8-5359-47e1-971c-542a9f8443ee

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HGVS expressions

NM_000038.6(APC):c.1902T>G (p.Ser634Arg)

NM_000038.6:c.1902T>G

NC_000005.10:g.112835109T>G

CM000667.2:g.112835109T>G

NC_000005.9:g.112170806T>G

CM000667.1:g.112170806T>G

NC_000005.8:g.112198705T>G

NG_008481.4:g.147589T>G

ENST00000502371.3:c.1567T>G

ENST00000504915.3:c.1956T>G

ENST00000505350.2:c.*1908T>G

ENST00000507379.6:c.1848T>G

ENST00000509732.6:c.1902T>G

ENST00000512211.7:c.1902T>G

ENST00000257430.9:c.1902T>G

ENST00000257430.8:c.1902T>G

ENST00000502371.2:c.255T>G

ENST00000504915.2:c.591T>G

ENST00000507379.5:c.1848T>G

ENST00000508376.6:c.1902T>G

ENST00000508624.5:c.*1224T>G

ENST00000512211.6:c.1902T>G

ENST00000520401.1:c.230+6137T>G

NM_000038.5:c.1902T>G

NM_001127510.2:c.1902T>G

NM_001127511.2:c.1848T>G

NM_001354895.1:c.1902T>G

NM_001354896.1:c.1956T>G

NM_001354897.1:c.1932T>G

NM_001354898.1:c.1827T>G

NM_001354899.1:c.1818T>G

NM_001354900.1:c.1779T>G

NM_001354901.1:c.1725T>G

NM_001354902.1:c.1629T>G

NM_001354903.1:c.1599T>G

NM_001354904.1:c.1524T>G

NM_001354905.1:c.1422T>G

NM_001354906.1:c.1053T>G
NM_001127510.3:c.1902T>G
NM_001127511.3:c.1848T>G
NM_001354895.2:c.1902T>G
NM_001354896.2:c.1956T>G
NM_001354897.2:c.1932T>G
NM_001354898.2:c.1827T>G
NM_001354899.2:c.1818T>G
NM_001354900.2:c.1779T>G
NM_001354901.2:c.1725T>G
NM_001354902.2:c.1629T>G
NM_001354903.2:c.1599T>G
NM_001354904.2:c.1524T>G
NM_001354905.2:c.1422T>G
NM_001354906.2:c.1053T>G

Uncertain Significance

Met criteria codes 2

BP1

PM2_Supporting

Not Met criteria codes 3

BP4

PS3

PS4

Evidence Links 1

Expert Panel

InSiGHT Hereditary Colorectal Cancer/Polypsis VCEP

Criteria Specification Information

[Criteria Specification:](#) ClinGen InSiGHT Hereditary Colorectal Cancer/Polypsis 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/Polypsis VCEP

The NM_000038.6(APC):c.1902T>G (p.Ser634Arg) variant in APC is a missense variant predicted to cause substitution of Serine by Arginine at amino acid position 634 (p.Ser634Arg). This variant has been reported in 1 proband meeting phenotypic criteria, resulting in a total phenotype score of 0.5 (PS4 not met [Ambry]). The variant has been reported in 1 additional proband with a colorectal cancer/polypsis associated phenotype not meeting phenotypic criteria (PMID: 27696107). The total minor allele frequency in gnomAD v2.1.1 (non-cancer) is 0.0004% (1/236788 alleles), which is lower than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polypsis VCEP (HCCP VCEP) threshold < 0.001% (0.00001) for PM2_Supporting if the allele count is ≤ 1 and therefore meets this criterion (PM2_Supporting). RT-PCR of cDNA and mini-gene splicing assays demonstrated that the variant impacts splicing by skipping of exon 15 resulting in a premature stop codon (PMID: 24599579). However, since alternative splicing/skipping of this exon is known and in PMID: 24599579 no pronounced skipping compared to controls is described, PS3 is not applicable. Moreover, the results from ≥ 2 in silico splicing predictors (SpliceAI and MaxEntScan) support that this variant does not affect splicing. APC, in which the variant was identified, is defined by the HCCP VCEP as a gene for which primarily truncating variants are known to cause disease (BP1). Due to conflicting evidence, 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: PM2_Supporting, BP1 (VCEP specifications version v2.0.3; date of approval 7/24/2023).

Met criteria codes

BP1			APC, in which the variant was identified, is defined by the HCCP VCEP as a gene for which primarily truncating variants are known to cause disease (BP1).
PM2_Supporting			The total minor allele frequency in gnomAD v2.1.1 (non-cancer) is 0.0004% (1/236788 alleles), which is lower than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP (HCCP VCEP) threshold < 0.001% (0.00001) for PM2_Supporting if the allele count is ≤ 1 and therefore meets this criterion (PM2_Supporting).
Not Met criteria codes			
BP4			The results from ≥ 2 in silico splicing predictors (SpliceAI and MaxEntScan) support that this variant does not affect splicing.
PS3			RT-PCR of cDNA and mini-gene splicing assays demonstrated that the variant impacts splicing by skipping of exon 15 resulting in a premature stop codon (PMID: 24599579). However, since alternative splicing/skipping of this exon is known and in PMID: 24599579 no pronounced skipping compared to controls is described, PS3 is not applicable.
			RT-PCR of cDNA and mini-gene splicing assay PubMed:24599579 
PS4			This variant has been reported in 1 proband meeting phenotypic criteria, resulting in a total phenotype score of 0.5 (PS4 not met [Ambry]). The variant has been reported in 1 additional proband with a colorectal cancer/polyposis associated phenotype not meeting phenotypic criteria (PMID: 27696107).

Curation History 	
    	
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