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Variant: NM_000038.6(APC):c.7489dup (p.Ser2497fs)

Version: 1.0

CA562217619

653103 (ClinVar)

Gene: APC (HGNC:324)
Condition: familial adenomatous polyposis 1 (MONDO:0021056)
Inheritance Mode: Autosomal dominant inheritance
UUID: e6f7176c-9897-4cb6-b594-c07a09e9054d
Approved on: 2025/5/16
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HGVS expressions

NM_000038.6:c.7489dup
NM_000038.6(APC):c.7489dup (p.Ser2497fs)
NC_000005.10:g.112843083dup
CM000667.2:g.112843083dup
NC_000005.9:g.112178780dup
CM000667.1:g.112178780dup
NC_000005.8:g.112206679dup
NG_008481.4:g.155563dup
ENST00000504915.3:c.7543dup
ENST00000505350.2:c.*7495dup
ENST00000507379.6:c.7435dup
ENST00000509732.6:c.7489dup
ENST00000512211.7:c.7489dup
ENST00000257430.9:c.7489dup
ENST00000257430.8:c.7489dup
ENST00000508376.6:c.7489dup
ENST00000520401.1:c.231-13566dup
NM_000038.5:c.7489dup
NM_001127510.2:c.7489dup
NM_001127511.2:c.7435dup
NM_001354895.1:c.7489dup
NM_001354896.1:c.7543dup
NM_001354897.1:c.7519dup
NM_001354898.1:c.7414dup
NM_001354899.1:c.7405dup
NM_001354900.1:c.7366dup
NM_001354901.1:c.7312dup
NM_001354902.1:c.7216dup
NM_001354903.1:c.7186dup
NM_001354904.1:c.7111dup
NM_001354905.1:c.7009dup
NM_001354906.1:c.6640dup
NM_001127510.3:c.7489dup
NM_001127511.3:c.7435dup
NM_001354895.2:c.7489dup
NM_001354896.2:c.7543dup
NM_001354897.2:c.7519dup

NM_001354898.2:c.7414dup
NM_001354899.2:c.7405dup
NM_001354900.2:c.7366dup
NM_001354901.2:c.7312dup
NM_001354902.2:c.7216dup
NM_001354903.2:c.7186dup
NM_001354904.2:c.7111dup
NM_001354905.2:c.7009dup
NM_001354906.2:c.6640dup

Pathogenic

Met criteria codes 3

PS4_Supporting PVS1 PM2_Supporting

Evidence Links 0

Expert Panel

InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP

Criteria Specification Information

Criteria Specification: *ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis 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/Polyposis VCEP

The NM_000038.6(APC):c.7489dup (p.Ser2497PhefsTer14) variant in APC is a frameshift variant located between codon 49 and 2645 and predicted to cause a premature stop codon in exon 16 in a gene in which loss-of-function is an established disease mechanism (PVS1). The total minor allele frequency in gnomAD v2.1.1 (non-cancer) is 0.0004% (1/236770 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). This variant has been reported in 1 family meeting phenotypic criteria, resulting in a total phenotype score of 1 (PS4_Supporting, Invitae internal data). Moreover, the variant has been reported in one additional proband with a colorectal cancer/polyposis associated phenotype not meeting phenotypic criteria and in three unaffected individuals with a family history of gastrointestinal cancer and/or colorectal polyps (Ambry Genetics and Invitae internal data). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal-dominant inherited FAP based on the ACMG/AMP criteria applied, as specified by the ClinGen HCCP VCEP: criteria PVS1, PS4_Supporting and PM2_Supporting applied (VCEP specifications version v2.0.3; date of approval 7/24/2023).

Met criteria codes

PS4_Supporting	✔	This variant has been reported in 1 family meeting phenotypic criteria, resulting in a total phenotype score of 1 (PS4_Supporting, Invitae internal data). Moreover, the variant has been reported in one additional proband with a colorectal cancer/polyposis associated phenotype not meeting phenotypic criteria and in three unaffected individuals with a family history of gastrointestinal cancer and/or colorectal polyps (Ambry Genetics and Invitae internal data).
PVS1	✔	The NM_000038.6(APC):c.7489dup (p.Ser2497PhefsTer14) variant in APC is a frameshift variant located between codon 49 and 2645 and predicted to cause a premature stop codon in exon 16 in a gene in which loss-of-function is an established disease mechanism (PVS1).

PM2_Supporting		✔	The total minor allele frequency in gnomAD v2.1.1 (non-cancer) is 0.0004% (1/236770 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).

Curation History

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