

Variant: *NM_000038.6(APC):c.1627G>T (p.Val543Phe)*

Version: 1.0

CA16024864 [↗](#)

490221 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 4b362109-ce61-450e-931e-aaa64c6a8657

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HGVS expressions

NM_000038.6:c.1627G>T

NM_000038.6(APC):c.1627G>T (p.Val543Phe)

NC_000005.10:g.112828856G>T

CM000667.2:g.112828856G>T

NC_000005.9:g.112164553G>T

CM000667.1:g.112164553G>T

NC_000005.8:g.112192452G>T

NG_008481.4:g.141336G>T

ENST00000502371.3:c.1409-6095G>T

ENST00000504915.3:c.1681G>T

ENST00000505084.2:n.1683G>T

ENST00000505350.2:c.*1633G>T

ENST00000507379.6:c.1573G>T

ENST00000509732.6:c.1627G>T

ENST00000512211.7:c.1627G>T

ENST00000257430.9:c.1627G>T

ENST00000257430.8:c.1627G>T

ENST00000502371.2:c.97-6095G>T

ENST00000504915.2:c.316G>T

ENST00000505084.1:n.114G>T

ENST00000507379.5:c.1573G>T

ENST00000508376.6:c.1627G>T

ENST00000508624.5:c.*949G>T

ENST00000512211.6:c.1627G>T

ENST00000520401.1:c.114G>T

NM_000038.5:c.1627G>T

NM_001127510.2:c.1627G>T

NM_001127511.2:c.1573G>T

NM_001354895.1:c.1627G>T

NM_001354896.1:c.1681G>T

NM_001354897.1:c.1657G>T

NM_001354898.1:c.1552G>T

NM_001354899.1:c.1543G>T

NM_001354900.1:c.1504G>T

NM_001354901.1:c.1450G>T

NM_001354902.1:c.1354G>T

NM_001354903.1:c.1324G>T

NM_001354904.1:c.1249G>T
NM_001354905.1:c.1147G>T
NM_001354906.1:c.778G>T
NM_001127510.3:c.1627G>T
NM_001127511.3:c.1573G>T
NM_001354895.2:c.1627G>T
NM_001354896.2:c.1681G>T
NM_001354897.2:c.1657G>T
NM_001354898.2:c.1552G>T
NM_001354899.2:c.1543G>T
NM_001354900.2:c.1504G>T
NM_001354901.2:c.1450G>T
NM_001354902.2:c.1354G>T
NM_001354903.2:c.1324G>T
NM_001354904.2:c.1249G>T
NM_001354905.2:c.1147G>T
NM_001354906.2:c.778G>T

Uncertain Significance

Met criteria codes 3

BP1 PM2_Supporting
PS3_Moderate

Not Met criteria codes 2

PS4 PP3

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.1627G>T variant in APC is a missense variant predicted to cause a substitution of valine by phenylalanine at amino acid position 543 (p.Val543Phe). This variant is located at the first base of exon 14. RT-PCR of the exons flanking the target site in a patient with AFAP shows that the variant c.1627G>T impacts splicing by leading to exon 14 skipping, which is an in-frame event (PS3_Moderate; PMID22987206). This variant scored 0.5 phenotype points based on information available in 3 individuals (PS4_variable not met; PMID 22987206, Invitae internal data). This variant is absent from gnomAD v2.1.1 (PM2_supporting). In silico predictions by SpliceAI, MaxEntScan and VarSEAK showed conflicting results (PP3 not met). APC is defined by the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel (HCCP VCEP) as a gene for which primarily truncating variants are known to cause disease (BP1). In summary, this is a Variant of Uncertain Significance (VUS) for FAP based on the ACMG/AMP criteria applied, as specified by the HCCP VCEP: BP1, PS3_moderate, and PM2_supporting. (VCEP specifications version 1; date of approval: 12/12/2022).

Met criteria codes

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).

PM2_Supporting



This variant is absent from gnomAD v2.1.1 (PM2_supporting).

PS3_Moderate			RT-PCR of exons flanking the target site in a patient with AFAP showed that the variant c.1627G>T impacts splicing by leading to exon 13 skipping (PMID22987206)(PS3_moderate).
Not Met criteria codes			
PS4			0.5 points based on phenotype information available in 3 individuals (PS4 not met, PMID 2298720, Invitae internal data).
PP3			varSEAK predicts class 5 slicing effect (16.38% that authentic splice site will be ineffective), MaxEntScan 4.43 (difference -1.86), SpliceAI showed no impact on splicing (0.01 for acceptor loss).

Curation History 			
			    
Showing 1 to 1 of 1 rows			

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