Version: 1.0

CA008769

816 (ClinVar)

Gene: APC
Condition: familial adenomatous polyposis 1 (MONDO:0021056)
Inheritance Mode: Autosomal dominant inheritance
UUID: 296f1801-94a5-465b-9e48-8c839bf73039
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HGVS expressions

NM_000038.6:c.3927_3931del
NC_000005.10:g.112839521_112839525del
CM000667.2:g.112839521_112839525del
NC_000005.9:g.112175218_112175222del
CM000667.1:g.112175218_112175222del
NC_000005.8:g.112203117_112203121del
NG_008481.4:g.152001_152005del
ENST00000502371.3:c.3592_3596del
ENST00000504915.3:c.3981_3985del
ENST00000505350.2:c.*3933_*3937del
ENST00000507379.6:c.3873_3877del
ENST00000509732.6:c.3927_3931del
ENST00000512211.7:c.3927_3931del
ENST00000257430.9:c.3927_3931del
ENST00000257430.8:c.3927_3931del
ENST00000502371.2:c.2280_2284del
ENST00000508376.6:c.3927_3931del
ENST00000508624.5:c.*3249_*3253del
ENST00000520401.1:c.230+10549_230+10553del
NM_000038.5:c.3927_3931del
NM_001127510.2:c.3927_3931del
NM_001127511.2:c.3873_3877del
NM_001354895.1:c.3927_3931del
NM_001354896.1:c.3981_3985del
NM_001354897.1:c.3957_3961del
NM_001354898.1:c.3852_3856del
NM_001354899.1:c.3843_3847del
NM_001354900.1:c.3804_3808del
NM_001354901.1:c.3750_3754del
NM_001354902.1:c.3654_3658del
NM_001354903.1:c.3624_3628del
NM_001354904.1:c.3549_3553del
NM_001354905.1:c.3447_3451del
NM_001354906.1:c.3078_3082del
NM_001127510.3:c.3927_3931del
NM_001127511.3:c.3873_3877del
NM_001354895.2:c.3927_3931del
NM_001354896.2:c.3981_3985del
NM_001354897.2:c.3957_3961del

NM_001354898.2:c.3852_3856del
NM_001354899.2:c.3843_3847del
NM_001354900.2:c.3804_3808del
NM_001354901.2:c.3750_3754del
NM_001354902.2:c.3654_3658del
NM_001354903.2:c.3624_3628del
NM_001354904.2:c.3549_3553del
NM_001354905.2:c.3447_3451del
NM_001354906.2:c.3078_3082del

Pathogenic

Met criteria codes 3

PM6_Strong PS4 PVS1

Not Met criteria codes 1

PM2

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.3927_3931del (p.Glu1309Aspfs*4) variant in APC is a variant predicted to cause a premature stop codon in exon 16 in a gene in which loss-of-function is an established disease mechanism (PVS1). This variant has been reported in more than 400 probands, resulting in a total phenotype score of 33 (PS4_VeryStrong, GeneDx, Ambry, Invitae, Catalan Institute of Oncology, University Hospital of Bonn, Leiden University Medical Center internal data). It has also been identified as a de novo occurrence with unconfirmed parental relationships in 63 individuals on LOVD and in 4 individuals from Barcelona internal data, the total points scored based on available phenotypic information is 17.5 (PM6_VeryStrong, LOVD, Catalan Institute of Oncology internal data). The highest allele frequency of this variant gnomAD v2.1.1 (non-cancer) is 0.000008456, which is higher than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel (HCCP VCEP) threshold of ≤ 0.000003 for PM2_Supporting (PM2_Supporting not met) and lower than the threshold (≥0.00001) for BS1 (BS1 not met). It is the most common pathogenic APC variant in APC InSiGHT LOVD (www.lovd.nl/APC; 331 / 5700 = 5.8%; retrieved on 06/01/2023), thus the occurrence in gnomAD is compatible with a pathogenic variant. In summary, this variant meets the criteria to be classified as Pathogenic for FAP based on the ACMG/AMP criteria applied, as specified by the HCCP VCEP: PVS1, PS4_VeryStrong, and PM6_VeryStrong (VCEP specifications version 1; date of approval: 12/12/2022).

Met criteria codes

PM6_Strong	✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 63 individual on LOVD and in 4 individual from Barcelona, the total points scored based on available phenotypic information is 17.5 (PM6_very strong, LOVD, Catalan Institute of Oncology).
PS4	✔	This variant has been reported in more than 400 probands, resulting in a total phenotype score of 33 (PS4_very strong, GeneDx, Ambry, Invitae, Catalan Institute of Oncology, University Hospital of Bonn, Leiden University Medical Center)
PVS1	✔	The c.3927_3931del (p.Glu1309AspfsTer4) variant in APC is a variant predicted/observed to cause a premature stop codon in biologically-relevant-exon 15 leading to nonsense mediated decay in a gene in which loss-of-function is an

established disease mechanism (PVS1).

Not Met criteria codes

PM2	✖	The highest population minor allele frequency of the variant c.3927_3931del in gnomAD v2.1.1 (non-cancer) is 0.000008456 (2/236524 alleles) in the Total population, which is higher than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis threshold threshold (≤ 0.000003) for PM2_supporting.

Curation History

Showing 1 to 1 of 1 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View		Pathogenic	Familial Adenomatous Polyposis 1	2023-03-14	1.0	-	APC

Showing 1 to 1 of 1 rows