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# *Variant: NM_000038.6(APC):c.4669_4670del (p.Thr1556_Ile1557insTer)*

Version: 1.0

*CA009682*

*183857 (ClinVar)*

**Gene**: APC (HGNC:324)
**Condition**: familial adenomatous polyposis 1 (MONDO:0021056)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** f7796bf0-f655-4344-947a-f1e08e323df1
**Approved on**: 2025/5/19
**Published on**: 2025/5/19

## *HGVS expressions*

**NM_000038.6:c.4669_4670del**
**NM_000038.6(APC):c.4669_4670del (p.Thr1556_Ile1557insTer)**
NC_000005.10:g.112840263_112840264del
CM000667.2:g.112840263_112840264del
NC_000005.9:g.112175960_112175961del
CM000667.1:g.112175960_112175961del
NC_000005.8:g.112203859_112203860del
NG_008481.4:g.152743_152744del
ENST00000504915.3:c.4723_4724del
ENST00000505350.2:c.*4675_*4676del
ENST00000507379.6:c.4615_4616del
ENST00000509732.6:c.4669_4670del
ENST00000512211.7:c.4669_4670del
ENST00000257430.9:c.4669_4670del
ENST00000257430.8:c.4669_4670del
ENST00000508376.6:c.4669_4670del
ENST00000508624.5:c.*3991_*3992del
ENST00000520401.1:c.230+11291_230+11292del
NM_000038.5:c.4669_4670del
NM_001127510.2:c.4669_4670del
NM_001127511.2:c.4615_4616del
NM_001354895.1:c.4669_4670del
NM_001354896.1:c.4723_4724del
NM_001354897.1:c.4699_4700del
NM_001354898.1:c.4594_4595del
NM_001354899.1:c.4585_4586del
NM_001354900.1:c.4546_4547del
NM_001354901.1:c.4492_4493del
NM_001354902.1:c.4396_4397del
NM_001354903.1:c.4366_4367del
NM_001354904.1:c.4291_4292del
NM_001354905.1:c.4189_4190del
NM_001354906.1:c.3820_3821del
NM_001127510.3:c.4669_4670del
NM_001127511.3:c.4615_4616del

NM_001354895.2:c.4669_4670del
NM_001354896.2:c.4723_4724del
NM_001354897.2:c.4699_4700del
NM_001354898.2:c.4594_4595del
NM_001354899.2:c.4585_4586del
NM_001354900.2:c.4546_4547del
NM_001354901.2:c.4492_4493del
NM_001354902.2:c.4396_4397del
NM_001354903.2:c.4366_4367del
NM_001354904.2:c.4291_4292del
NM_001354905.2:c.4189_4190del
NM_001354906.2:c.3820_3821del

**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.4669_4670del (p.Ile1557Ter) variant in APC is a nonsense 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 0.000004 (1/250082 alleles), which is lower than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP (HCCP VCEP) threshold of < 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 proband meeting phenotypic criteria, resulting in a total phenotype score of 1 point (PS4_Supporting [PMID: 17135276]). The variant is reported in two additional probands with a colorectal cancer/polyposis associated phenotype not meeting phenotypic criteria (PMID: 15108288 and LOVD individual ID 00014662). 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 HCCP VCEP: criteria PVS1, PS4_Supporting and PM2_Supporting applied (VCEP specifications v2.0.3; date of approval 7/24/2023).**

**Met criteria codes**

| | | |
|---|---|---|
| **PS4_Supporting** | ✔ | This variant has been reported in 1 proband meeting phenotypic criteria, resulting in a total phenotype score of 1 point (PS4_Supporting [PMID: 17135276]). The variant is reported in two additional probands with a colorectal cancer/polyposis associated phenotype not meeting phenotypic criteria (PMID: 15108288 and LOVD individual ID 00014662). |
| **PVS1** | ✔ | |

The NM_000038.6(APC):c.4669_4670del (p.Ile1557Ter) variant in APC is a nonsense 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 0.000004 (1/250082 alleles), which is lower than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP (HCCP VCEP) threshold of < 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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