Inactivation of the APC Gene Is Constant in Adrenocortical Tumors from Patients with Familial Adenomatous Polyposis but Not Frequent in Sporadic Adrenocortical Cancers

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Abstract

Purpose: In adrenocortical tumors (ACT), Wnt/β-catenin pathway activation can be explained by β-catenin somatic mutations only in a subset of tumors. ACT is observed in patients with familial adenomatous polyposis (FAP) with germline APC mutations, as well as in patients with Beckwith-Wiedemann syndrome with Wilms' tumors reported to have WTX somatic mutations. Both APC and WTX are involved in Wnt/β-catenin pathway regulation and may play a role in ACT tumorigenesis. The aim of this study was to report if APC and WTX may be associated with FAP-associated and sporadic ACT.

Experimental Design: ACTs from patients with FAP and sporadic adrenocortical carcinomas (ACC) with abnormal β-catenin localization on immunohistochemistry but no somatic β-catenin mutations were studied. APC was analyzed by denaturing high-performance liquid chromatography followed by direct sequencing and by multiplex ligation–dependent probe amplification when allelic loss was suspected. WTX was studied by direct sequencing.

Results: Four ACTs were observed in three patients with FAP and were ACC, adrenocortical adenoma, and bilateral macronodular adrenocortical hyperplasia, all with abnormal β-catenin localization. Biallelic inactivation of APC was strongly suggested by the simultaneous existence of somatic and germline alterations in all ACTs. In the 20 sporadic ACCs, a silent heterozygous somatic mutation as well as a rare heterozygous polymorphism in APC was found. No WTX mutations were observed.

Conclusions: ACT should be considered a FAP tumor. Biallelic APC inactivation mediates activation of the Wnt/β-catenin pathway in the ACTs of patients with FAP. In contrast, APC and WTX genetic alterations do not play a significant role in sporadic ACC. Clin Cancer Res; 16(21); 5133–41. ©2010 AACR.

Several studies support the importance of activation of the Wnt/β-catenin pathway in adrenocortical tumorigenesis, as previously shown also in a variety of cancers (1–3). Gene profiling studies have reported overexpression of target genes in the Wnt/β-catenin pathway in adrenocortical carcinoma (ACC; ref. 4) as well as in adrenocorticotropic-independent macronodular adrenocortical hyperplasia (AIMAH; ref. 5). It seems that activation of this pathway may play an important role in adrenocortical tumorigenesis through activating mutations of the β-catenin gene (CTNNB1) in adrenocortical adenoma (ACA), ACC, and primary pigmented micronodular adrenal dysplasia (PPNAD; refs. 1–3). This is demonstrated by the frequent nuclear and cytoplasmic β-catenin accumulation on immunohistochemistry (1–3). Currently, β-catenin–activating mutations are the most frequent genetic defect observed in sporadic ACA and ACC (1, 3). However, somatic β-catenin–activating mutations are present in only a quarter to a third of ACCs (1). This strongly suggests the possible existence of alternative genetic defects or crosstalks with other signaling pathways that could activate the Wnt/β-catenin signaling pathway.

Familial adenomatous polyposis (FAP; OMIM #175100) is an autosomal dominant inherited disorder characterized by an early onset of hundreds to thousands of adenomatous polyps throughout the colon and rectum.
Translational Relevance

Activation of the Wnt/β-catenin pathway frequently occurs in adrenocortical tumors (ACT). This is explained by β-catenin somatic mutations but only in a subset of tumors, suggesting the possible involvement of other genetic defects. Our results support that ACT tumorigenesis, at least in patients with familial adenomatous polyposis (FAP), can be mediated by biallelic APC inactivation leading to activation of the Wnt/β-catenin pathway. Thus, ACT should be considered a FAP tumor, and screening for ACT should be included in the workup of patients with FAP.

Materials and Methods

Patients and tissue collection

Patients with FAP and ACT. Three FAP patients from two different families, who presented with four ACTs, including one bilateral AIMAH, one ACA, and one ACC, were included in this study.

Patients with sporadic ACC. Twenty sporadic ACC samples presenting Wnt/β-catenin pathway activation (i.e., nuclear and/or cytoplasmic β-catenin protein accumulation by immunohistochemistry) but no somatic β-catenin–activating mutation were studied.

For all samples, clinical, hormonal, and radiological investigations were done as previously reported (27, 28). Tumor and tissue fragments obtained during surgery were immediately dissected by a pathologist and then frozen and stored in liquid nitrogen until use.

The study was carried out under the approval of the Institutional Review Board (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) of Cochin Hospital, Paris, France. Informed consent was obtained for clinical information, tumor analysis, and genetic diagnosis as part of the COMETE network research activities.

Table 1. Characteristics of the three patients with ACTs in the context of FAP

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)/sex</th>
<th>Side</th>
<th>Secretion</th>
<th>Pathologic diagnosis</th>
<th>Gross aspect (weight in g and diameter in cm)</th>
<th>Weiss score</th>
<th>β-Catenin immunohistochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (mother)</td>
<td>59/F</td>
<td>Right</td>
<td>Glucocorticoid</td>
<td>AIMAH</td>
<td>6 g, 3 cm (3 nodules)</td>
<td>NA</td>
<td>Diffuse cytoplasmic accumulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left</td>
<td></td>
<td>AIMAH</td>
<td>18 g, 7 cm (including several nodules, with one of 25 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (son)</td>
<td>29/M</td>
<td>Right</td>
<td>Mineralocorticoid and glucocorticoid</td>
<td>ACA</td>
<td>32 g, 5 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>68/F</td>
<td>Right</td>
<td>None</td>
<td>ACC</td>
<td>230 g, 12 cm</td>
<td>6</td>
<td>Cytoplasmic and nuclear accumulation</td>
</tr>
</tbody>
</table>

(Continued on the following page)
Pathology examination and immunohistochemistry

For each patient, diagnosis was confirmed by pathologic examination, and a Weiss score established when appropriate (29, 30). Immunohistochemical staining for β-catenin was done as previously described (1, 2) and assessed in a blinded fashion with respect to the mutational status and clinical data. β-Catenin immunohistochemistry was evaluated for the presence of cytoplasmic and nuclear staining. Cytoplasmic and/or nuclear staining on immunohistochemistry was recorded as intracellular accumulation.

Nucleic acid extraction and mutation analysis of CTNNB1, the mutation cluster region, APC, and WTX

DNA was extracted from peripheral blood leukocytes using the Wizard Genomic DNA Purification Kit (Promega Corp.), and tumor DNA was purified by cesium chloride gradient ultracentrifugation (31). Because mutations of the main proteins in the Wnt/β-catenin pathway are reported to be exclusive (32), specimens were first sequenced for mutations in CTNNB1; if absent, this was followed by sequencing for mutations in APC, and then WTX. For mutation analysis, PCR was used to amplify the exon 3 and flanking 5' intron sequences of CTNNB1 in the tumors (1); the mutation cluster region of APC in the tumors and leukocytes of patients with FAP; and WTX in the tumors (see Supplementary Data). Both strands of the amplified products were directly sequenced on an automated sequencer (ABI 3700, Perkin-Elmer). Nucleotides were numbered in accordance with the reference sequences of CTNNB1 (GenBank accession no. NM_001904), APC (GenBank accession no. NM_001127510), and WTX (GenBank accession no. NM_152424).

Denaturing high-performance liquid chromatography analysis

When two mutations were not found in the mutation cluster region of APC, denaturing high-performance liquid chromatography (DHPLC), optimized for rapid screening of the 15 exons and splice junctions of the APC gene, was used to screen for mutations. Touchdown PCR was used to reduce nonspecific primer annealing by gradually lowering the annealing temperature as PCR cycling progressed. Amplifications were done using the Optimase polymerase (Transgenomic). Following PCR, reaction products were denatured by heating at 94°C for 5 minutes, followed by cooling at 25°C over a 25-minute period to enhance heteroduplex formation. Five microliters of PCR products were analyzed directly by DHPLC using the WAVE DNA fragment analysis system (Transgenomic) with 1 to 3 injections per amplicon, for a total of 71 injections for a complete analysis. Abnormal profiles detected by DHPLC were subsequently sequenced using the BigDye Terminator reaction kit on the ABI Prism 3100 genetic analyzer system (Applied Biosystems). Primer sequences and annealing temperatures for PCR and analysis parameters for DHPLC are listed in Supplementary Data.

Multiplex ligation–dependent probe amplification

When large deletions or loss of heterozygosity was suspected, APC was screened using the multiplex ligation–dependent probe amplification (MLPA) using the SALSA P043 kit (MRC-Holland), which had 23 probe sets for the APC region. In short, 120 ng of genomic DNA were used as starting material, and after hybridization at 60°C for 16 hours followed by ligation and amplification, the PCR products were separated on a 16-channel ABI Prism 3100 genetic analyzer (Applera) using capillary electrophoresis. Fragment analysis, normalization of data by regression line of control probe, and quantitative and statistical analysis were done using three methods, GeneMapper (Applera), GeneMarker (Softgenetics), and Excel (Microsoft), using normalization by the regression line of the control probe. All three methods yielded similar results.

Table 1. Characteristics of the three patients with ACTs in the context of FAP (Cont’d)

<table>
<thead>
<tr>
<th>Patient</th>
<th>CTNNB1 somatic mutation</th>
<th>APC germline mutation</th>
<th>APC somatic mutation (additional tumor mutation)</th>
<th>WTX somatic mutation</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (mother)</td>
<td>None</td>
<td>c.4549_4550ins6 (GTGTAAG/p.Glu1517fsX1519) (heterozygous state)</td>
<td>c.1863_1866del4 (TTAC; heterozygous state)</td>
<td>None</td>
<td>Alive</td>
</tr>
<tr>
<td>2 (son)</td>
<td>None</td>
<td>c.4549_4550ins6 (GTGTAAG/p.Glu1517fsX1519) (heterozygous state)</td>
<td>c.4667_4668insA/p.Thr1556fsX1558 (heterozygous state)</td>
<td>None</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>c.3234 T&gt;A/p.Tyr1078X (heterozygous state)</td>
<td>None</td>
<td>None</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Abbreviation: NA, nonapplicable.
*No APC gene deletion detected by MLPA.
Results

ACTs in patients with FAP

Three patients from two different families with FAP were identified and presented with four various ACTs including one ACA, one ACC, and a bilateral AIMAH (Table 1). On β-catenin immunohistochemistry, all tumors showed diffuse cytoplasmic and/or nuclear accumulation, revealing activation of the Wnt/β-catenin pathway (Fig. 1). There were no somatic CTNNB1 mutations, but all of the tumors showed evidence of germline and somatic APC mutations according to Knudson’s two-hit model for a tumor suppressor gene (Fig. 2).

Patients 1 and 2 were mother and son belonging to the same family with FAP that had been characterized by a heterozygous germline mutation (c.4549_4550ins6/p.Glu1517fsX1519) in both the blood cells and tumors. Patient 1 had AIMAH, and in this patient, a heterozygous

![Image of histology](https://clincancerres.aacrjournals.org/content/16/21/5136/F1.large.jpg)
Deletion (c.1863_1866del4/p.Thr621fsX628) was detected in the main nodule of the right adrenal gland, and a heterozygous insertion (c.4667_4668insA/p.Thr_1556fsX1558) was detected in the main nodule of the left gland (Fig. 3A). Unfortunately, nodules smaller than 2 mm were not available for sequencing.

In patient 2, who had ACA, tumor analysis was surprising for a homozygous germline \textit{APC} mutation (c.4549_4550ins6/p.Glu1517fsX1519). An analysis of known intragenic polymorphisms of \textit{APC} detected a change of status between the blood cells, which were heterozygous for the mutation, and the tumor, which was homozygous. Partial or complete \textit{APC} gene deletion was ruled out by MLPA, which detected 2 copies of the gene. This homozygous status in the tumor could be attributed to large genomic rearrangements with loss of the normal allele and duplication of the mutated allele involving at least the entire \textit{APC} gene (Fig. 3B).

With regard to patient 3, who was not related to the other patients and had ACC, a heterozygous germline mutation (c.4689_4690ins4/p.Leu1563fsX1567) was detected in both the blood cells and tumor. An additional heterozygous somatic mutation (c.3234T>A/p.Tyr1078X) was also found in the tumor.

Overall, five known silent single-nucleotide polymorphisms (http://www.umd.be/APC/ and http://www.ensembl.org) were observed in the four tumors as well as the corresponding germline DNA.

### Table 2

<table>
<thead>
<tr>
<th>ACT Characteristics</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twenty cases of sporadic ACC</td>
<td>Identified and characterized to have Wnt/(\beta)-catenin pathway activation (i.e., abnormal (\beta)-catenin localization by immunohistochemistry but no somatic (\beta)-catenin activating mutations); the data are presented in Table 2. During sequencing for \textit{APC}, a silent heterozygous variant (c.3340C&gt;A/p.Arg1114Arg) that had not been described previously was discovered. In another tumor, there was a rare heterozygous polymorphism (c.3949G&gt;C/p.Glu1317Gln) that might represent a colonic adenoma-carcinoma predisposition allele (33–36). These two variants were found in the DNA of both the leukocytes and tumors. In addition, four tumors were homozygous for all single-nucleotide polymorphisms analyzed, and no large deletions were found on MLPA, excluding a hemizygous status. Additionally, 11 known heterozygous single-nucleotide polymorphisms without any amino acid modification were observed in 16 tumors. The frequency of these polymorphisms was similar to that in the general population according to National Center for Biotechnology Information databases (<a href="http://www.umd.be/APC/">http://www.umd.be/APC/</a> and <a href="http://www.ensembl.org">http://www.ensembl.org</a>). Of the 20 sporadic ACC analyzed, none had any somatic WTX mutations, and 5 known polymorphisms of \textit{WTX} (<a href="http://www.ensembl.org">http://www.ensembl.org</a>) were observed in all these tumors.</td>
</tr>
</tbody>
</table>
Discussion

This study shows that APC inactivation is one of the mechanisms of Wnt/β-catenin pathway activation in adrenocortical tumorigenesis. The important role of the Wnt/β-catenin pathway in ACT is supported by gene profiling studies showing overexpression of target genes in ACC (4) as well as AIMA (5) and PPNAD (37). Activation of this pathway is often associated with loss of heterozygosity in ACT tissues.

Fig. 3. Details of germline and somatic mutations including polymorphisms in patients 1 and 2. A, mutations and polymorphisms in patients 1 and 2. B, hypothesis for the second-hit mutation in patient 2 (the son). Because no deletions were found on MLPA, a duplication of the mutated allele in the tumor cells was likely.
pathway can be explained by somatic CTNNB1 mutations of β-catenin in a subset of ACA, ACC, and PPNAD (1-3, 38). From immunohistochemical and molecular studies, it is likely that activation of the Wnt/β-catenin pathway is a major event in ACC (1, 39). As it is observed more frequently than somatic CTNNB1 mutations (1, 2), activation of the pathway could be explained by other genetic defects such as APC or WTX mutations.

Our results showed that all ACTs in patients with FAP presented with a secondary somatic alteration of the APC gene, in addition to the germline mutation. All somatic mutations led to a stop codon, resulting in a truncated APC protein. This is consistent with the finding that the residual allele of the APC gene is inactivated in tumors of patients with FAP (40) and suggests that ACT can be mediated by biallelic APC inactivation.

The majority of APC mutations are nucleotide substitutions and frameshift mutations that result in truncated proteins. Interestingly, uncommon APC mutations were observed in patients with FAP in our study. According to the APC mutation database (http://www.umd.be/ APC/), none of the mutations in our study have been described previously. Moreover, one of them presented with a mutation [c.4549-4550ins6 (GTGTGA)/p.Glu1517fsX1519] in the homozygous state with a diploid APC copy number on MLPA. This suggests the loss of the normal allele with a duplication of the mutated APC locus. As previously shown in FAP, loss of heterozygosity tends to occur by a mechanism that does not result in a change of the APC gene dosage, with a diploid APC copy number, probably because of chromosome rearrangement tied to mitotic recombination (41). Overall, this is consistent with the previously reported high incidence of chromosomal gains, frequently on chromosome 5 where the APC locus is located (42). Interestingly, a similar mechanism of loss of the wild-type allele has been described in a functional ACT from a patient with FAP, which was associated with a nonsense germline mutation at codon 1577 (17). Overall, the simultaneous existence of somatic and germline alterations was found in all ACTs from patients with FAP that were analyzed in our series.

APC promoter methylation has been shown to silence transcription and has therefore been proposed as an alternative mechanism of inactivation of APC (43). This mechanism may be involved in sporadic ACCs, which do not carry the APC or CTNNB1 mutation. Nevertheless, this mechanism can be ruled out as the dominant mechanism. Indeed, no decrease in APC mRNA expression was observed in our previously published gene expression profiling microarray in which APC mRNA expression was compared in ACC with the CTNNB1 mutation, ACC without the CTNNB1 mutation, ACA, and normal adrenal gland (44).

The higher incidence of adrenal lesions in patients with FAP patients in retrospective studies, such as those by Smith and colleagues (7) from St. Mark’s Hospitals and by Marches and colleagues (8) from the Cleveland Clinic Foundation, could have been attributed to the extensive and frequent imaging done in these expert, high-volume centers. Our study is the largest series of patients with genetic analysis and gives strong molecular evidence for a causal association between ACT and FAP. Indeed, we believe that ACT tumorigenesis, at least in patients with FAP, can be mediated by biallelic APC inactivation and thus complete loss of function of the APC gene according to Knudson’s two-hit model (45). The abnormal cytoplasmic and nuclear β-catenin localization on immunohistochemistry confirms the activation of the pathway in the ACTs with APC mutations in our study. Further experimental studies with APC knockdowns in mice will help toward a better understanding of APC-mediated ACT tumorigenesis.

Given the present genetic findings and the previous findings that ACT was more prevalent in patients with FAP by 7.4% to 13% than the general population (7, 8), ACT should be considered a FAP tumor. Therefore, screening for ACT could be offered to patients with FAP. Although no evidence-based recommendations on screening (i.e., methods for screening, the frequency and intervals, and the age at which it should start) for ACT are available, our suggestion would be to consider an initial screening by abdominal magnetic resonance imaging before adolescence.

Table 2. Characteristics of the 20 patients with sporadic ACCs

<table>
<thead>
<tr>
<th>Status</th>
<th>n (%)/ mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive without recurrence</td>
<td>8</td>
</tr>
<tr>
<td>Alive with recurrence</td>
<td>0</td>
</tr>
<tr>
<td>Dead</td>
<td>12</td>
</tr>
</tbody>
</table>

| Follow-up (mo) | 44 (1-119) |
| Local or regional manifestations | 2          |
| Secretion      |            |
| Cortisol + androgen | 6          |
| Cortisol        | 4          |
| Nonsecreting    | 4          |
| Cortisol + mineralocorticoid        | 2          |
| Cortisol + mineralocorticoid + androgen | 1        |
| Cortisol + precursor                 | 1          |
| Androgen                 | 1          |
| Cortisol + precursor + androgen    | 1          |
| Tumor size (cm)            | 10.5 (4-24) |
| Tumor weight (g)            | 314 (40-2160) |
| Age at diagnosis (y)        | 44 (18-68)    |
| Sex ratio (male/female)     | 5/15         |
| Side (right/left)           | 10/10        |
| Presentation at diagnosis    |             |
| Endocrine features           | 16          |
| Local or regional manifestations | 2         |
| Incidentaloma                | 4           |

Our study is the largest series of patients with frequent imaging done in these expert, high-volume centers, could have been attributed to the extensive and frequent imaging done in these expert, high-volume centers.
which would simultaneously screen for other extraintestinal manifestations such as desmoid tumors, pancreatic cancer, and hepatomas. Referral to an endocrinologist would be another option for patients with a significant family history of extraintestinal manifestations and would facilitate physical examination for any thyroid nodules in the surveillance for thyroid carcinoma. Special attention to the adrenal glands should be given to these patients at each interval imaging. Owing to improved survival as a result of better prevention of colorectal cancer, the incidence of extraintestinal manifestations, including ACT, will further increase. Education of medical personnel to these rare manifestations would be the best way to avoid adverse consequences.

One limitation of our study is the small number of patients with FAP and ACT, as the combination is uncommon. Consequently, our findings cannot be generalized to the ACTs in all patients with FAP. Yamakita and colleagues (46) suggested that second-hit mutations are not always found in ACT from FAP. Because most of the previous genetic data on ACTs in patients with FAP are not available, we cannot rule out some unrelated sporadic adrenal disease. It is also possible that some APC mutations in FAP create a mutant protein displaying a tissue-specific dominant negative effect (47, 48) by reducing the function of the APC tumor suppressor wild-type allele in the adrenal cortex. Such a germline mutation conferring a particular genetic susceptibility to tumor development has been hypothesized in thyroid carcinomas associated with FAP (6), which usually occur in the absence of biallelic inactivation of the APC gene. Nevertheless, to date, no specific familial, gender, or genotype association that increases the risk of ACT has been described. An association of desmoid tumors and ACTs has been suggested in FAP (8), but the evidence for such an association remains weak (7).

The results of our genetic study of APC in sporadic ACC contrasted with that in FAP-associated ACT. All the sporadic ACC tumors studied presented with activation of the Wnt/β-catenin pathway on immunohistochemistry. In this way, they were similar to the ACTs in patients with FAP. However, only two changes in the APC gene were found in 20 cases of sporadic ACC. These two genetic alterations were a silent variant and a rare polymorphism, and therefore, their functional or pathologic value remains questionable and probably minor. Furthermore, these changes presented in both the tumor and germline DNA and were not associated with secondary alterations of the APC gene at the somatic level. APC has already been implicated in other tumors with Wnt/β-catenin pathway activation, such as sporadic hepatocellular carcinoma (49). Our results do not exclude that biallelic APC inactivation could still occur in some rare sporadic ACC with Wnt/β-catenin pathway activation. Our study also indicates that the somatic mutations of WTX that are observed frequently in Wilms’ tumors do not play a significant role in sporadic ACC in adults. This suggests that along with somatic β-catenin mutations, other genetic or epigenetic defects could explain the Wnt/β-catenin pathway activation in sporadic ACC in adults. One explanation would be activation of the Wnt/β-catenin pathway by the overexpression of its extracellular ligands. Crosstalks with other signaling pathways such as the insulin-like growth factor pathway, which frequently overexpresses insulin-like growth factor II in these tumors (49), might be another explanation.

In conclusion, our results support that ACT tumorigenesis, at least in patients with FAP, can be mediated by biallelic APC inactivation leading to activation of the Wnt/β-catenin pathway. ACT should be considered a FAP tumor and might be screened during the workup of patients with FAP. The role of the APC or WTX gene in sporadic ACC remains to be seen, but these genes do not seem to play a significant role.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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