

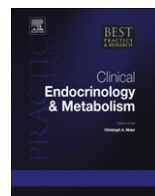


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5

### Pathogenesis of benign adrenocortical tumors

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Most adrenocortical tumors (ACT) are benign unilateral adrenocortical adenomas, often discovered incidentally. Exceptionally, ACT are bilateral. However bilateral ACT have been very helpful to progress in the pathophysiology of ACT. Although most ACT are of sporadic origin, they may also be part of syndromic and/or hereditary disorders. The identification of the genetics of familial diseases associated with benign ACT has been helpful to define somatic alterations in sporadic ACT: for example, identification of *PRKAR1A* mutations in Carney complex or alterations of the Wnt/ $\beta$ -catenin pathway in Familial Adenomatous Polyposis Coli. Components of the cAMP signaling pathway—for example, adrenocorticotrophic-hormone receptors and other membrane receptors, Gs protein, phosphodiesterases and protein kinase A—can be altered to various degrees in benign cortisol-secreting ACT.

These progress have been important for the understanding of the pathogenesis of benign ACT, but already have profound implications for clinical management, for example in unraveling the genetic origin of disease in some patients with ACT. They also have therapeutic consequences, and should help to develop new therapeutic options.

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## Introduction

Adrenal masses are most often discovered as adrenal incidentalomas that are present in 1–7% of the general population and are, by definition, discovered incidentally during general investigations.<sup>1</sup> Most turn out to be benign adrenocortical adenomas (ACA), that can cause hypersecretion (hypercortisolism in Cushing's syndrome, mineralocorticoid excess in Conn's adenoma) or be non-functional. Bilateral ACT (adrenocortical tumors) are less frequent but have been very useful to progress in the understanding of the pathogenesis of ACT.<sup>2</sup> They are observed in two rare situations, either of which can induce steroid oversecretion: primary pigmented nodular adrenocortical disease (PPNAD) and adrenocorticotrophic-hormone (ACTH)-independent macronodular adrenal hyperplasia (AIMAH).<sup>3,4</sup>

Progress in this field has been slower than that for most other tumors, mainly because of the limited number of ACT treated surgically. However, considerable advances toward understanding the pathogenesis of ACT development have been made the last 15 years. This progress is the result of a combination of various strategies: identification of responsible genes in some rare familial diseases; investigation of signaling pathways that have proved important in other endocrine (or non-endocrine) tumors; and also close clinical observation. Initially, the study of rare genetic syndromes associated with ACT has greatly facilitated progress and has increased our understanding of the genetics of sporadic benign and malignant ACT.<sup>5</sup>

Here we discuss these advances in the genetics and the signaling alterations observed in benign unilateral and bilateral ACT. We will first describe genetic alterations observed initially as germline defects in genetic syndromes predisposing to benign ACT and found out later to be also altered at the somatic level, therefore limited to the tumor tissue, in sporadic ACT. Some of these genetic alterations occur on key component of signaling pathways, and we will then describe the signaling alterations observed in benign ACT, focusing mainly on the cAMP and the Wnt signaling pathways.

## The genetics of benign adrenocortical tumors

The study of familial syndromes associated with ACT has led to the identification of genes involved in the development of these tumors (Table 1). In turn, these genes occasionally show somatic defects in sporadic ACT, the clinical and biological phenotypes of which may mimic those observed in their "familial counterparts". This notion may be of great practical help for the development of molecular tools for the diagnosis and management of ACT. At present most of the genetic alterations known in ACT have been discovered by this approach.

### *Carney complex, PRKARIA, and the 17q22-24 locus*

Carney complex ([CNC]; MIM 160980) is a dominantly inherited disorder with a variety of clinical and pathological manifestations.<sup>6–8</sup> The main characteristics of CNC are spotty skin-pigmentation (lentiginosis), endocrine overactivity and cardiac myxomas. ACTH-independent Cushing syndrome due to PPNAD is the main endocrine manifestation of CNC. PPNAD can be also isolated in some patients without other CNC manifestations or familial history.

CNC seems a genetically heterogeneous disease and linkage analysis has shown that at least two loci are involved: 2p16 and 17q22-24. The gene located on 17q22-24 has been identified as that encoding the protein kinase A (PKA) regulatory subunit 1A (*PRKARIA*).<sup>9,10</sup> *PRKARIA* is a key component of the cAMP signaling pathway, which has been implicated in endocrine tumorigenesis (see below). Heterozygous inactivating mutations of *PRKARIA* are found in about two third of families with CNC.<sup>11</sup> In CNC tumors allelic losses (LOH) at 17q22-24 have been demonstrated, suggesting that *PRKARIA* is normally a tumor suppressor gene. Interestingly, patients with isolated PPNAD and apparently no or little evidence for a family history of CNC can also present a germline mutation of *PRKARIA*.<sup>12,13</sup> Interestingly a hot spot *PRKARIA* mutations seems to predispose to isolated PPNAD.<sup>14</sup>

In sporadic ACT, somatic *PRKARIA* mutations have been found in a subset of hormone-secreting ACA; these ACA present with clinical, biological, and pathological features similar to those in PPNAD.<sup>15</sup> LOH at 17q22-24 has also been observed in sporadic ACT.

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