

Pituitary pathology in patients with Carney Complex: growth-hormone producing hyperplasia or tumors and their association with other abnormalities

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Abstract First described in the mid 80's, Carney Complex (CNC) is a rare, dominantly heritable disorder with features overlapping those of McCune-Albright syndrome (MAS) and other multiple endocrine neoplasia (MEN) syndromes like MEN type 1 (MEN 1). Pituitary tumors have been described in a number of patients with CNC; they present with elevated growth hormone (GH) levels and mild hyperprolactinemia. However, most patients with CNC have mild hyper-somatotrophinemia starting in adolescence; this is similar to the situation in MAS patients: in both disorders, pituitary hyperplasia appears to precede tumor development. Familial pituitary tumor syndromes such as CNC provide an important insight into the genetics and molecular pathology of pituitary and other endocrine tumors. Our understanding of these conditions is expanding rapidly due to the identification of the causative genes and the availability of murine disease models. The present report reviews the clinical findings related to pituitary tumor development among patients with CNC and provides an update on murine models of the complex.

Keywords Carney complex · Multiple endocrine neoplasias · Pituitary tumors · Growth hormone · Prolactin · Acromegaly · *PRKARIA* · Cyclic AMP

Introduction

A complex of spotty-skin pigmentation, myxomas (Fig. 1), and endocrine overactivity, associated with a variety of other tumors was described by Carney in the mid-1980s [1–5]. Carney complex (CNC), a rare condition, has been described in about 500 people to date and is caused in more than 60% of the cases that meet diagnostic criteria by an inactivating mutation in the gene encoding protein kinase A (PKA) type 1A regulatory ($R1\alpha$) subunit (*PRKARIA*) at 17q22–24; a second, as yet uncharacterized, locus at 2p16 has also been implicated in some families [6, 7]. The pituitary gland is frequently affected in CNC and the clinical features are reminiscent of McCune-Albright syndrome (MAS) [8–11]: despite frequent abnormalities of growth hormone (GH), insulin-like growth factor 1 (IGF-1), and prolactin (PRL) secretion, clinical acromegaly or significant hyperprolactinaemia and growing GH- or PRL-producing tumors are rare [12–15]. Mouse models of $R1\alpha$ deficiency have been created but they failed to reproduce a specific or a significant pituitary phenotype, although mild abnormalities were seen. This review outlines the current state of knowledge regarding pituitary pathology in CNC and related mouse models.

Clinical and histopathological analysis of the pituitary in CNC patients

GH-producing tumors have been identified so far in several CNC patients with clinically diagnosed acromegaly at the National Institutes of Health [16]. Acromegaly in this condition is characterized by a slow, progressive course (Fig. 2). The mean age of acromegaly was 35.8 years in the cohort of patients that we recently reported [16, 17]. It is interesting that in many of these patients clinically significant

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Fig. 1 Spotty skin pigmentation on the face of a patient with CNC can be scarce (A) and is primarily characterized by lentigines on the nose and around the eyes, on the vermillion border of the lips and on the cheeks; (B) physical examination may identify subcutaneous nodules that are slowly growing myxomas (arrow), and (C) other pigmented lesions such as blue nevi (arrow)

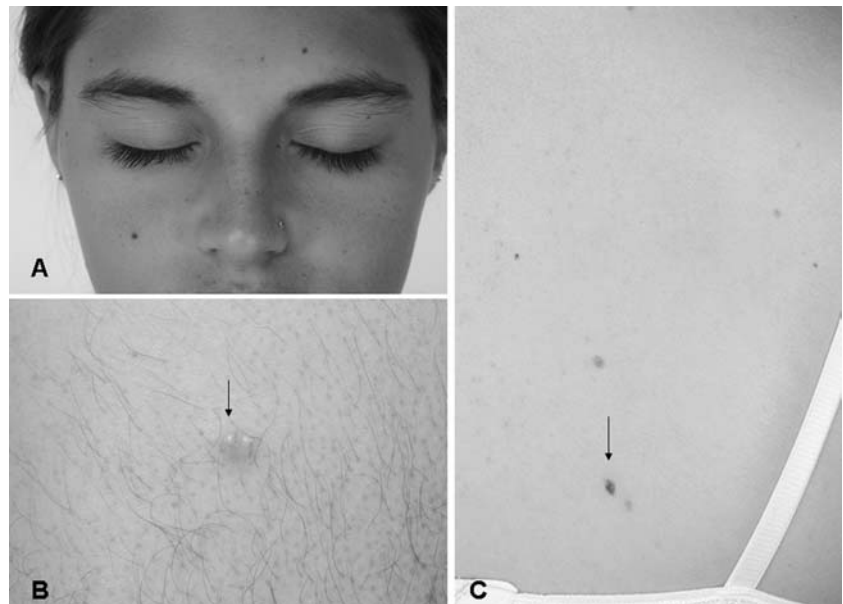


Fig. 2 A patient with CNC and acromegaly: the MRI after contrast enhancement showed multiple microadenomas (arrows). The pituitary was removed almost entirely because multiple small tumors were iden-

tified in the background of hyperplasia. The tumor of this patient was extensively studied and its histologic and ultrastructural features reported by Bossis et al. [28]

acromegaly did not become apparent until after they were operated for their Cushing syndrome: 72% of these patients had at the same time primary pigmented nodular adrenocortical disease (PPNAD) (Table 1). A change in clinical phenotype in a patient that has concurrently Cushing syndrome and acromegaly is not unexpected given the known relationship between GH and cortisol metabolism [18], but the phenomenon has not been studied in detail in CNC or patients with similar conditions (i.e. MAS).

Among the patients with CNC and acromegaly that were operated for their pituitary tumors, there have been at least four (4) to date who had evidence of GH- and PRL-producing cell hyperplasia on their pituitary histopathology: their GH-producing cells stained positive for PRL. Staining for α -subunit, β -TSH and β -LH was also present in diffusely and

rarely present cells of some adenomas and within foci of normal cells entrapped within the tumors. On the other hand, ACTH and FSH staining, when obtained, could only be seen in foci of normal cells entrapped within the tumors or the hyperplasia [17].

In these patients, the extra-tumoral pituitary parenchyma showed evidence of adenohypophyseal hyperplasia that was characterized by poorly delineated zones with increased cellularity and an expanded, somewhat irregular reticulin pattern. A zone of probable transition from hyperplasia to adenoma, characterized by the gradual disappearance of the reticulin pattern and increasing cellularity, was also documented in these cases. Both hyperplastic and adenomatous tissue stained for GH and PRL in all patients [16, 17] (Fig. 2) indicating that the process involves undifferentiated

Table 1 Clinical manifestations of CNC patients with acromegaly

Patient	Age	Gender	Cardiac myxomas			Skin myxomas			Breast myxomas			Other pigmented lesions			LCCSCT	Schwannoma	Malignancy	Thyroid tumors	Thyroid cancer	Ovarian lesions
			Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No						
CAR 001.02	42	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		Yes	Yes	Yes	
CAR 001.05	55	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		Yes	Yes	Yes	
CAR 001.07	40	m	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 001.08	31	m	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 001.10	60	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 003.01	65	m	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 005.03	40	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 007.01	70	m	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 007.04	56	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 007.05	55	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 007.07	34	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 016.02	52	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 020.03	41	m	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 029.03	39	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 033.02	45	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 034.01	63	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 034.02	39	m	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 102.06	54	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 102.13	47	m	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 110.01	46	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 515.01	16	m	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 540.01	60	m	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 550.01	30	f	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 564.03	49	m	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
CAR 568.01	49	m	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	
N (%)			16 (64%)		13 (52%)	9 (36%)	25 (100%)	22 (88%)	18 (72%)	8 (32%)	7 (28%)	10 (40%)	13 (52%)	3 (12%)	7 (28%)		10 (40%)	13 (52%)	3 (12%)	7 (28%)

Abbreviations: PPNAD: Primary pigmented nodular adrenal cortical disease, LCCSCT: Large cell calcifying Sertoli cell tumors, f = female, m = male.

somatotrophic cells. Of particular interest, as we have reported in the study by Pack et al. [16] was the finding of tumor multicentricity. Further supporting the notion of hyperplasia developing into an adenoma was the gross finding of multiple macroscopic tumors at the surface of the gland in at least one of the cases.

The above suggestions were supported by genetic studies: complex genetic abnormalities were detected by comparative genomic hybridization (CGH) in a large and rapidly growing but otherwise benign GH- and PRL-producing adenoma that appeared to grow in the background of hyperplasia in a 19-year-old patient with CNC. There were no such abnormalities detected in the normal and the hyperplastic tissue surrounding the tumor [16]. This observation is consistent with the concept that clonal expansion of genetically transformed somatic cells [19] underlies pituitary tumor development in CNC patients, which appears to also be the case in MAS [20–23] but not in MEN 1, unless associated with elevated GHRH levels [24].

What does one do with patients with CNC that have elevated GH and/or IGF-1? Since most of the patients have some abnormality of GH secretion due to the underlying pathologic abnormality of pituitary hyperplasia it is essential to identify these patients with clinically significant acromegaly, as defined by commonly applied criteria [25]. In the latter group, there will be few patients that have an aggressively growing tumor such as the one reported by Pack et al. [16] and others [26] that will require surgery and other treatment



Fig. 3 Classic acromegaly in a patient with CNC who required irradiation for cure of his hypersomatotropinemia. The patient eventually died from pancreatic cancer, one of the tumors possibly linked to CNC

as needed (Fig. 3). Most CNC patients, however, will have negative pituitary imaging studies; it has been our practice to treat these patients with somatostatin analogues with the ultimate goal of normalizing their IGF-1 levels, consistent with common practice [27]. Most of the remaining patients with CNC have abnormal responses to oral glucose tolerance test (oGTT) but normal IGF-1 and normal pituitary imaging: we continue to follow these patients annually by magnetic resonance imaging (MRI) and oGTT; if a tumor develops it is treated surgically, whereas if IGF-1 levels increase without a visible tumor we start somatostatin analogue therapy. This approach has been so far successful and none of the CNC patients that are described in Table 1 has gone to develop severe complications from his/her acromegaly. Also, only one of our patients with acromegaly required irradiation treatment (Fig. 3) for ultimate cure pointing, perhaps, to an overall more benign course of this disease in the context of CNC (data not shown).

Electron microscopy studies

In 2002, Kurtkaya-Yapicier O et al. studied two pituitary tumors from CNC patients; interestingly the two tumors were quite different at the ultrastructural level: the first patient had an adenoma immunoreactive for GH and PRL and the two hormones were present in the same secretory granules. In contrast, the tumor of the second patient consisted of GH-immunoreactive, sparsely granulated cells [24]. The nuclei were ovoid or variably irregular and possessed a well-to-extensively developed nucleolus as well as small quantities of stippled heterochromatin. Rough endoplasmic reticulum was abundant and Golgi complexes were conspicuous, occupied a large portion of the cytoplasm [24]. The ultrastructural variability of CNC-associated pituitary tumors was again shown in yet another tumor that was studied by Bossis et al. [28]: the excised pituitary was covered by small and bigger tumors that showed variable but concurrent immunostaining for GH, PRL or LH (Fig. 2).

Human genetics: the role of the *PRKARIA* gene

The CNC-associated pituitary tumors studied to date from patients with inactivating *PRKARIA* mutations have demonstrated LOH for the 17q22–24 *PRKARIA* locus [6, 16]. So far 17 of our CNC patients and acromegaly have had mutations of the *PRKARIA* gene that result in premature stop codons for the predicted protein sequence; another 5 patients have been found to have *PRKARIA* mutations that lead to an expressed (but abnormal) protein. We could not identify *PRKARIA* mutations in 3 patients with acromegaly and CNC [29] (Fig. 4).

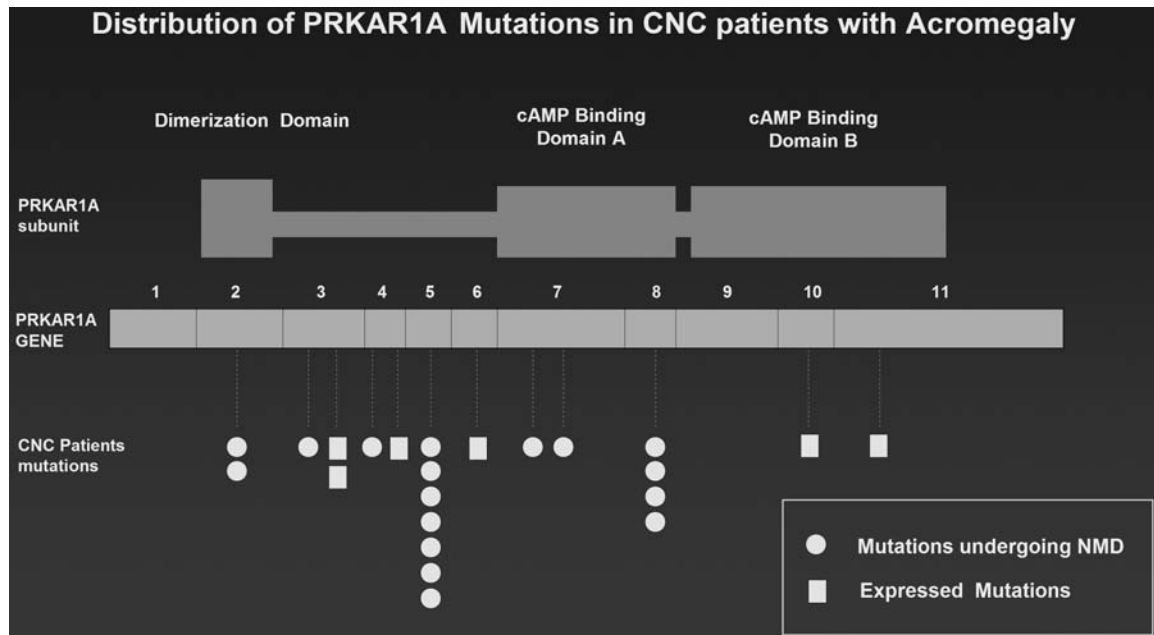


Fig. 4 Mutations of the *PRKAR1A* gene in patients with CNC and acromegaly

There have been no other gene studies of pituitary tissue from patients with CNC that do not carry germline *PRKAR1A* mutations. CGH analysis of 3 CNC-associated micro-adenomas showed no significant changes over normal DNA [16]. Analysis of the most aggressive tumor, an invasive macroadenoma, showed multiple changes, including losses of chromosomal regions 6q, 7q, 11p, 11q, and gains of 1pter-p32, 2q35-qter, 9q33-qter, 12q24-qter, 16, 17, 19p, 20p, 20q, 22p, 22q [16]. The greatest contiguous changes were losses of the long arm of chromosome 6 and the entire chromosome 11. A more recent CGH study of an additional number of CNC-associated pituitary tumors confirmed the losses of part or all of 1p and 11q chromosomal regions [30].

No mutations of the *PRKAR1A* gene have been found in more than 150 sporadic GH-secreting or other pituitary tumors [31–33]. However, there is recent evidence that low levels of the R1 α protein in tumor cells may lead to an imbalance in the ratio between the type 1 and 2 regulatory subunits of PKA and favor cAMP-dependent proliferation in somatotrophs [34].

Isolated *prkar1a* deficiency does not lead to mouse pituitary tumors

Three mouse models of *prkar1a* deficiency have been developed [35–38]: they developed some of the tumors associated with CNC but none developed any pituitary abnormalities. More specifically, a transgenic mouse bearing an antisense construct of the *prkar1a* exon 2 (X2AS) developed multiple endocrine abnormalities in parallel to some of the features

of CNC. It also developed a host of other tumors suggesting that *PRKAR1A* may indeed function as a tumor suppressor gene as it had been suggested by the allelic losses in human pituitary and other tumors [35, 36].

Two *prkar1a* heterozygote knock-out [KO] models have also been developed [37, 38]. No endocrine abnormalities were seen; pituitary tumors were not found although sarcomas (some with myxomatous differentiation) and schwannomas frequently developed in these rodents [37, 38].

The pituitary glands of both the *prkar1a* X2AS and heterozygote KO mice were examined recently [39]: mild abnormalities were indeed seen and an excess of GH-producing cells was confirmed [40]. In the absence of any tumors or other structural abnormalities, a cross between the transgenic MT-GHRH acromegalic mouse [41] and the *prkar1a* heterozygote KO mouse model was developed in our laboratory [42]. Preliminary analysis showed that in the presence of a tumorigenic, proliferative signal such as that of GHRH, *prkar1a* deficiency was associated with more significant somatomammotroph hyperplasia [43, 44].

Conclusions

Patients with CNC have mild hypersomatotropinemia that is due to pituitary GH- and PRL-producing cell hyperplasia and which only rarely leads to frank acromegaly and tumor formation. *PRKAR1A* deficiency is associated with growth of pituitary cells *in vitro* but deficiency of this gene in rodents is only permissive for pituitary abnormalities: it requires another factor, such as for example GHRH.

Other genes leading to similar phenotypes in both humans and rodents remain to be identified.

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