

# Carney Complex

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## ABSTRACT

The complex of myxomas, spotty skin pigmentation, and endocrine over activity or Carney complex (CNC) (MIM no. 160980) is an autosomal dominant disorder that was described in 1985 by Carney. The diagnosis of CNC is made if two of the main manifestations of the syndrome are present, these need to be confirmed by histology, biochemical testing, or imaging. Alternatively, the diagnosis is made when one of the criteria is present and the patient is a carrier of a known inactivating mutation of the PRKAR1A gene. Most cases of CNC are caused by inactivating mutations in the gene encoding one of the subunits of the protein kinase A (PKA) tetrameric enzyme, namely regulatory subunit type1 alpha (PRKAR1A), located at 17q22-24. Endocrine, dermatologic, and cardiac anomalies are the main manifestations of CNC. Skin abnormalities are present in almost 77% of the CNC patients. Variety of endocrine gland tumors are observed in CNC patients, namely growth hormone secreting pituitary adenoma (acromegaly), thyroid adenomas or carcinomas, testicular tumors (large cell calcifying sertoli cell tumors), and ovarian cyst. Cardiac myxoma is the most common primary tumor affecting the heart, accounting for nearly half of cardiac neoplasms. Approximately, 30-60% of CNC patients will develop cardiac myxoma, usually at much younger ages than the sporadic tumors. A high degree of suspicion, complete evaluation, genetic counseling is important aspect of management of Carney's disease. Once confirmed, surgical removal remains the mainstay of treatment.

**Keywords:** CNC, Molecular genetics, Cardiac myxoma, Primary pigmented nodular adrenocortical disease, PRKAR1A gene.

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## INTRODUCTION

The complex of myxomas, spotty skin pigmentation, and endocrine over activity or CNC (MIM no. 160980) is an autosomal dominant disorder that was described in 1985 by Carney.<sup>1,2</sup> More than 500 index cases have been reported; since then worldwide and majority of them (almost 70%) presented with positive family history.<sup>3,4</sup>

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Several patients described in earlier years under the acronyms NAME (nevi, atrial myxomas, and ephelides) and LAMB (lentiginos, atrial myxomas, and blue nevi) probably had CNC.<sup>5,6</sup> The median age at detection is 20 years. But, the initial presentation varies with patients. Life expectancy of patients with CNC is decreased mainly due to heart-related causes, which accounts for 57% of deaths of CNC patients.<sup>7</sup>

The most common features of CNC include spotty skin pigmentation (lentiginos, freckling, café-au-lait spots, and blue nevi), myxomas of the heart, skin, and breast, and primary pigmented nodular cortical hyperplasia associated with an atypical form of Cushing's syndrome.<sup>8,9</sup>

The diagnosis of CNC is made if two of the main manifestations of the syndrome are present,<sup>10</sup> these need to be confirmed by histology, biochemical testing, or imaging. Alternatively, the diagnosis is made when one of the criteria is present and the patient is a carrier of a known inactivating mutation of the PRKAR1A gene.<sup>10,11</sup>

## Molecular Genetics of CNC

As most of the index case run in the families, suspicion was that CNC is a familial disease. Investigation revealed that CNC is an autosomal dominant disorder that was described in 1985 as "the complex of myxoma, spotty pigmentation, and endocrine overactivity in 40 patients."<sup>1</sup> Most cases of CNC are caused by inactivating mutations in the gene encoding one of the subunits of the protein kinase A (PKA) tetrameric enzyme, namely regulatory subunit type1 alpha (PRKAR1A), located at 17q22-24.<sup>7</sup>

Another locus (2p16) has been implicated, but sequencing of the region in the linked families did not reveal alterations in coding sequences.<sup>12</sup>

Cyclic AMP (c-AMP) dependant PKA, a serine/threonine kinase, is the main mediator of c-AMP signalling in mammals.<sup>13</sup> Phosphorylation mediated by the c-AMP/PKA signalling pathway can be elicited by various physiological ligands in cells and is critically involved in the regulation of metabolism, cell proliferation, differentiation, and apoptosis.<sup>14</sup> The PKA holoenzyme is composed of genetically distinct catalytic (C) and regulatory (R) subunits. They form the tetrameric holoenzyme R2C2 that dissociates in the presence of c-AMP into an R2 (c-AMP) 4 dimer and two free catalytically active C subunits.<sup>15</sup> The best known function of the R subunits *in vitro* is inhibition of C subunit kinase activity.<sup>16</sup> There are four major R subunit isoforms (R1a, R1b, R2a, and R2b) and three isoforms of the C subunit (Ca, Cb,

and Cy) have been identified. The free catalytic subunits that are active serine threonine kinases further phosphorylate a series of targets that regulate downstream regulator enzymes, ion channels and activate the transcription of specific genes mediating the cell growth and differentiation.<sup>17</sup> PRKAr1a haploinsufficiency in turn causes excess cellular c-AMP signalling in affected areas, causing CNC tumorigenesis.<sup>18</sup>

PRKAR1A is a key component of the c-AMP signalling pathway that has been implicated in endocrine tumorigenesis. Mutations in PRKAR1A are seen in more than 70% of patients with classical CNC and in the majority of the cases they lead to complete inactivation of one of the PRKAR1A alleles as a result of premature stop codon generation and subsequent nonsense-mediated mRNA decay (NMD). The most frequent PRKAR1A mutation in CNC is a deletion that results in frame shift (c.578delTG in exon 4B of the gene).<sup>19,20</sup>

In CNC patients with Cushing's syndrome, the frequency of PRKAR1A mutation is about 80%, suggesting that families with primary pigmented nodular adrenocortical disease (PPNAD) are more likely to carry a 17q22-24 defect.<sup>2</sup> Patients with isolated PPNAD with no familial history of CNC may also carry a germ line *de novo* mutation in PRKAR1A.<sup>22</sup> In CNC, patient's loss of heterozygosity (LOH) at 17q 22-24 may be observed suggesting that PRKAR1A is a tumor suppressor gene.

According to Knudson's hypothesis, tumor suppressors, unlike oncogenes generally operate in a recessive manner, requiring loss of both copies for tumorigenesis.<sup>23</sup> PRKAR1A gene does not seem to follow the definition of a classic tumor suppressor gene (TSG), as discussed earlier; R1a is frequently increased in several cancers. In contrast, CNC is a multiple neoplasia syndrome results from loss of R1a expression. Thus, PRKAR1A could perhaps have properties of both oncogene and tumor suppressor gene but satisfies the criteria for neither in human and nor in mouse oncogenesis.<sup>23</sup>

**Table 1:** Clinical features of Carney complex

Main features of CNC	Percentage (%)
Primary pigmented nodular adrenocortical disease	25-60
Cardiac myxoma	30-60
Skin myxoma	20-63
Lentiginosis	60-70
Multiple blue nevus	
Breast ductal adenoma	25
Testicular tumor	33-56
Ovarian cyst in female	20-67
Acromegaly	10
Thyroid tumor	10-25
Melanotic schwannoma	8-18
Osteochondromyxoma	<10

CNC: Carney complex

A putative CNC2 gene located at 2p16 locus remains to be determined. Somatic alterations of the 2p16 region have been reported in CNC tumors even in patients with mutation of the CNC1 gene (i.e., PRKAR1A located on 17q22-24).<sup>24</sup> These alterations are usually gene amplification suggesting that the gene located at 2p16 is a potential oncogene.<sup>25</sup>

In conclusion, regarding PKA "role in CNC, Bossis et al, beautifully laid down the following sentences. 'PKA holoenzyme is involved in several process including signal transduction, cell cycle regulation, chromosomal stability, and cellular homeostasis. It is still not clear whether regulatory subunit of PRKAR1A act as tumor suppressor gene, oncogene, or merely acts by modulating the levels of PKA activity. Haploinsufficiency of PRKAR1A leads to an increase in kinase activity; the latter appears to be associated with the multiple tumor formation and tendency for carcinogenesis in CNC. It may be well that dysregulation of the PKA tetramer rather than levels of a particular subunit are the mediator of tumorigenesis.'<sup>26</sup>

### Clinical Description of CNC

Endocrine, dermatologic, and cardiac anomalies are the main manifestation of CNC.

Main features of CNC are presented in Table 1.

### Skin Lesions

Skin abnormalities are present in almost 77% of the CNC patients.<sup>28</sup> The most common skin lesions are spotty skin pigmentations (lentiginosis), epithelioid blue nevi, and skin myxomas. Skin lesions in CNC are important because of their high diagnostic value, presentation in early life, and easily recognizable.

Lentigo is a hamartomatous melanocytic lesion clinically similar but histologically different from freckles. The number of the lesion may vary from few to myriads.<sup>1,7,27</sup>

Morphologically, they are flat, poorly circumscribed, brown to black macules usually less than 0.5 cm in diameter but may differ in different ethnic groups.<sup>28</sup> Histologically, lentiginosis show basal cell layer hyperpigmentation associated with an increased number of melanocytes (hyperplasia), the majority of which appear hypertrophic. Freckles are different from lentiginosis as they present with regular number of melanocyte and get pigmented due to increased melanin production and deposition in surrounding keratinocytes.

Lentiginosis is one of the cardinal features of CNC that can appear early in life, but they usually acquire their typical intensity and distribution during peripubertal period.<sup>4,29,30</sup>

Lentiginosis are usually seen on the face (the periocular and perioral zones including the vermilion border of the lips), the eyelids and the conjunctiva of sclera, the trunk, and the hands and fingers. They have also been observed on the feet,

the vulva, the anal verge, and the glans penis.<sup>31</sup> In contrast to age-related skin lesions, CNC-associated lentiginos tend to fade after the 4th decade of life but may be detectable as late as the 8th decade.<sup>29,32</sup>

Blue nevus is the 2nd most common occurring skin lesion in CNC patients. They are seen as small usually smaller than 5 mm, blue to black colored marks with circular or star-shaped appearance. Face trunk and limbs are usually affected more than hands or feet. An interesting variety of blue nevi is epitheloid blue nevus (EBN) which is sometimes seen with CNC. EBN usually presents with intensive pigmentation and poorly circumscribed proliferative regions. EBN has two cell types namely heavily pigmented globular and fusiform cells, and lightly pigmented polygonal spindle melanocyte. Epitheloid blue nevi has no dermal fibrosis. Anyway, EBN is not considered pathognomonic for CNC but simply associated with the disease.<sup>29,32</sup>

The third most common skin manifestation of CNC is cutaneous myxoma, is reported between 30 and 55% of the studied patients.<sup>4,29</sup> They do occur on the eyelid (most common site), the external ear canal, the nipple, and the oropharynx. They usually appear as asymptomatic, sessile, small, opalescent or dark pink papules, and large finger-like

pedunculated lesions. They appear early in life but most common during teen years. In the majority of cases, cutaneous myxoma show multiple appearances and a tendency to recur. Histologically, skin myxomas consist of basophilic ground substance (myxoid stroma) with few macrophages or bland spindle cells, forming poorly or well-lobulated dermal masses with widely spaced capillaries.

### Endocrine Manifestation

The variety of endocrine gland tumors are observed in CNC patients namely growth hormone secreting pituitary adenoma (acromegaly), thyroid adenomas or carcinomas, testicular tumors (large cell calcifying sertoli cell tumors), and ovarian cyst.

Adrenocorticotrophic hormone (ACTH) independent Cushing's syndrome due to PPNAD is seen in 25 to 30% of patients with CNC. However, histologic evidence of PPNAD has been reported in almost every patient with CNC who underwent autopsy.<sup>7</sup> The disease was named after macroscopic appearance of the adrenals that is characterized by the small pigmented micronodules observed in the cortex.<sup>26</sup> PPNAD usually presents in the 2nd or 3rd decade of life without demonstrating female predilection seen in adult patient with

**Table 2:** Diagnostic criteria of Carney complex (*Courtesy:* Constantine A Stratakis)

#### Major diagnostic criteria for CNC

1. Spotty skin pigmentation with typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosal).
2. Myxoma\* (cutaneous and mucosal).
3. Cardiac myxoma\*.
4. Breast myxomatosis\* or fat suppressed MRI findings suggestive of this disorder.
5. PPNAD\* or paradoxical positive response of urinary glucocorticoid excretion to dexamethasone administration during liddle's test.
6. Acromegaly due to Gh producing adenoma\*.
7. LCCST\* or characteristic calcification on testicular ultrasound.
8. Thyroid carcinoma\* or multiple, hypochoic nodules on thyroid ultrasound in a young patient.
9. Psammomatous melanotic schwannomas\*.
10. Blue nevus, EBN.
11. Breast ductal adenoma\*.
12. Osteochondromyxoma\*.

#### Supplementary criteria

1. Affected first-degree relative.
2. Inactivating mutation of the PRKAR1A gene.

#### Finding suggestive of or possible associated with CNC but not diagnostic for the disease

1. Intense freckling (without darkly pigmented spots or typical distribution).
2. Blue nevus, common type (if multiple).
3. Cafe Au lait spots or other birthmarks.
4. Elevated IGF-I levels, abnormal GTT, or paradoxical Gh response to TRH testing in the absence of clinical acromegaly.
5. Cardiomyopathy.
6. Pilonidal sinus.
7. History of Cushing's syndrome, acromegaly, or sudden death in extended family.
8. Multiple skin tags or other skin lesions, lipoma.
9. Colonic polyps (usually in association with acromegaly).
10. Hyperprolactinemia (usually mild and always combined with clinical or subclinical acromegaly).
11. Single, benign thyroid nodule in a young patient: multiple thyroid nodules in an older patient (detected on ultrasound).
12. Family history of carcinoma, in particular of the thyroid, colon, pancreas, and ovary; other multiple benign or malignant tumors.

\*After historical confirmation. CNC: Carney complex; Gh: Growth hormone; GTT: Glucose tolerance test; LCCST: Large cell calcifying sertoli cell tumor; MRI: Magnetic resonance imaging; PPNAD: Primary pigmented nodular adrenocortical disease, TGF: Transforming growth factor- $\beta$ 1; TRH: Thyroid-releasing hormone

Cushing's syndrome.<sup>33</sup> Though rare, it can occur before the age of 4 years and rarely diagnosed after the age of 40 years. The disease is usually bilateral with primary involvement of both adrenals.

The hypercortisolism due to PPNAD may manifest as classic Cushing's syndrome or isolated features like mild growth retardation, severe precocious osteoporosis, and severe muscle and skin wasting.<sup>33</sup> Cyclical or atypical Cushing's syndrome is also common among patients with CNC. Urinary cortisol is increased in most patients at the time of diagnosis of PPNAD but its levels can be variable. Patient with PPNAD have low plasma levels of ACTH and show no stimulation of cortisol or ACTH secretion after corticotropin release hormone injection. In addition, dexamethasone fails to suppress cortisol secretion with high dose challenge.

Macroscopically adrenals are usually small, with multiple dark brown or black nodules (0.5-5 mm) and microscopically numerous nonencapsulated cortical nodules with large amount of lipofuscin responsible for their pigmentation and pathognomonic cortical atrophy.

Computed tomography (CT) images with slice thickness of 5 or 10 mm usually miss the lesion mainly due to small overall size of the adrenals and small size of the pigmented nodules (0.5-3 mm).

CT images if obtained with slice thickness of 3 mm or less, with and without contrast material, small, round, well delineated, hypodense and numerous pigmented nodular lesion could be seen. Iodocholesterol scintigraphy when performed usually shows a bilateral uptake despite ACTH suppression by endogenous hypercortisolism.

Systemic screening in patients with CNC or screening in familial cases can also lead to diagnosis of PPNAD.

The incidence of growth hormone producing pituitary tumors and clinical acromegaly has been estimated at less than 15% patients with CNC.<sup>34</sup> Acromegaly presenting as a primary manifestation of the CNC usually has pituitary macroadenomas, otherwise it presents as a slow progressive clinical course.<sup>31</sup>

Clinical thyroid disorder is rare though evaluation with ultrasonography may reveal some pathology in over 60% patients, which is much more in comparison with general population screening.<sup>31</sup> Broad-spectrum thyroid pathology has been described in CNC patients starting from follicular hyperplasia to follicular or papillary carcinoma.

Testicular tumors, the most frequent being primary large cell calcifying sertoli cell tumor (LCCSCT) are easily detected by ultrasonography as bilateral microcalcifications. Ovarian cysts and cystadenoma have been observed in CNC patients.

## Cardiac Myxoma

Cardiac myxoma is the most common primary tumor affecting the heart, accounting for nearly half of cardiac neoplasms.<sup>35</sup>

Approximately, 30 to 60% of CNC patients will develop cardiac myxomas,<sup>25</sup> usually at much younger ages than the sporadic tumors. The natural history of sporadic cardiac myxoma characterized by a predilection for the left atrium of the heart and occurs in 75% of the cases, mainly in middle-aged women and arising usually from interatrial septum at the border of fossa ovalis with a recurrence rate of approximately 3%. Familial form of cardiac myxomas are characterized by younger age of presentation, predominantly in males, multifocal in nature, and involvement of one or more chambers of heart and in unusual location. They are also characterized by high incidence of recurrence after resection.

As a cardinal feature of CNC, cardiac myxomas are responsible for the death of more than 50% of patients, either from tumors themselves or from postsurgical complications.<sup>7</sup> The size, mobility, and location determine the clinical manifestation of the tumor. The typical triad includes intracardiac obstruction, embolic events, and constitutional symptoms.

Cardiac myxomas may be cause of the high rate of (16%) sudden death historically reported in CNC families, thus underlying the importance of its early diagnosis. Regular screening with ultrasound in CNC patients and families is of paramount importance for early detection and prevention of morbidity and mortality. The echocardiographic appearance is a useful diagnostic tool in early diagnosis, with high sensitivity. The transesophageal and transthoracic echocardiography are able to determine tumor size and type, anatomical localization, and valvular abnormalities.<sup>36,37</sup> CT and magnetic resonance imaging (MRI) have excellent diagnostic advantage regarding tumor delineation and spread. An MRI currently appears to be imaging modality of choice in differentiating left atrial myxoma from malignancies.<sup>38</sup> On sonography, heart myxomas which may vary from few millimeters to 8 cm in diameter appear as isoechoic masses inside cardiac chambers. On T2-weighted MRI images, they appear as hyperintense lesion compared with myocardium.

A definite diagnosis of CNC is given if two or more major manifestations are present.<sup>7,11,25,30</sup> A number of related manifestations may accompany or suggest the presence of CNC but are not considered diagnostic of the disease.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with CNC, the following evaluations are recommended:

- Imaging or biochemical screening for endocrine tumors for diagnostic purposes only.
- Thyroid ultrasonography recommended as a satisfactory, cost-effective method for determining thyroid involvement in pediatric and young adults with CNC. Its value, however, is questionable in older individuals.

- In males, testicular ultrasonography at the initial evaluation.
- In females, transabdominal ultrasonography during the first evaluation. Unless an abnormality is detected initially, the test need not be repeated because of the low risk for ovarian malignancy.
- Medical genetics consultation.

#### *Treatment of Manifestations of CNC*

- Cardiac myxoma: Open-heart surgery
- Cutaneous and mammary myxoma—surgical excision
- Cushing's syndrome: Bilateral adrenalectomy
- Pituitary adenoma: Trans-sphenoidal surgery
- Thyroid adenomas: Surgery if cancerous
- Large-cell calcifying sertoli cell tumor: Orchiectomy usually required for boys with LCCSCT and gynecomastia to avoid premature epiphyseal fusion and induction of central precocious puberty.
- Psammomatous melanotic schwannomas (PMS): Surgery to remove primary and/or metastatic lesions.

#### *Prevention of Primary Manifestations*

The only preventive measure in an asymptomatic individual is surgical removal of a heart tumor (cardiac myxoma) prior to the development of heart dysfunction, stroke, or other embolism.

#### *Prevention of Secondary Complications*

Development of metabolic abnormalities from Cushing's syndrome or arthropathy and other complications from acromegaly may be prevented by medical or surgical treatment of the respective endocrine manifestations.

#### *Surveillance*

Recommended clinical surveillance for individuals with CNC includes the following:

##### *Prepubertal Pediatric Individuals*

- Echocardiogram (annually; biannually for those with a history of excised myxoma).
- Testicular ultrasound for boys; close monitoring of growth rate and pubertal staging (annually).

##### *Postpubertal Pediatric and Adult Individuals*

- Echocardiogram (annually or biannually for adolescent individuals with a history of excised myxoma).
- Testicular ultrasound (annually).
- Thyroid ultrasound (baseline examination—may be repeated as needed).
- Transabdominal ultrasound of the ovaries (baseline examination—may be repeated as needed).

- Urinary-free cortisol levels (annually).
- Serum insulin-like growth factor-1 levels (annually).

#### *Further Evaluation of Affected Individuals of All Age Groups as needed*

For primary pigmented nodular adrenocortical disease, in addition to urinary-free cortisol levels:

- Diurnal cortisol levels (11:30 PM, 12:00 AM and 7:30 AM, 8:00 AM sampling).
- Dexamethasone-stimulation test.
- Adrenal CT.

#### *For Gigantism/Acromegaly, in Addition to Serum IGF-1 Levels*

- Pituitary MRI
- 3-hour oral glucose tolerance test (OGTT)
- 90-minute thyroid-releasing hormone (TRH) testing.

#### *For Psammomatous Melanotic Schwannoma*

MRI of brain, spine, chest, abdomen, retroperitoneum, and pelvis to be done for evaluation in affected individual of all age groups.

#### *Evaluation of Relatives at Risk*

When a clinically diagnosed relative has undergone molecular genetic testing and is found to have a mutation in PRKARIA, molecular genetic testing can be used with certainty to clarify the genetic status of at-risk family members so that they can be evaluated promptly for treatable manifestations.

#### *Genetic Counseling*

CNC is inherited in an autosomal dominant manner. Approximately, 70% of individuals diagnosed with CNC have an affected parent; approximately, 30% have a *de novo* mutation. Each child of an individual with CNC has a 50% chance of inheriting the mutation. Prenatal testing for pregnancies at increased risk is possible if the disease-causing mutation in the family is known.

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