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GENETICS OF ENDOCRINE DISEASE

Clinical and Molecular Features of the Carney Complex: Diagnostic Criteria and Recommendations for Patient Evaluation

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Carney complex is a multiple neoplasia syndrome featuring cardiac, endocrine, cutaneous, and neural tumors, as well as a variety of pigmented lesions of the skin and mucosae. Carney complex is inherited as an autosomal dominant trait and may simultaneously involve multiple endocrine glands, as in the classic multiple endocrine neoplasia syndromes 1 and 2. Carney complex also has some similarities to McCuneAlbright syndrome, a sporadic condition that is also characterized by multiple endocrine and nonendocrine tumors. Carney complex shares skin abnormalities and some nonendocrine tumors with the lentiginoses and certain of the hamartomatoses, particularly Peutz-Jeghers syndrome, with which it shares mucosal lentiginosis and an unusual gonadal tumor, large-cell calcifying Sertoli cell tumor. Careful clinical analysis has enabled positional cloning efforts to identify two chromosomal loci harboring potential candidate genes for Carney complex. Most recently, at the 17q22–24 locus, the tumor suppressor gene *PRKAR1A*, coding for the type 1α regulatory subunit of PKA, was found to be mutated in approximately half of the known Carney complex kindreds. *PRKAR1A* acts a classic tumor suppressor gene as demonstrated by loss of heterozygosity at the 17q22–24 locus in tumors associated with the complex. The second locus, at chromosome 2p16, to which most (but not all) of the remaining kindreds map, is also involved in the molecular pathogenesis of Carney complex tumors, as demonstrated by multiple genetic changes at this locus, including loss of heterozygosity and copy number gain. Despite the known genetic heterogeneity in the disease, clinical analysis has not detected any corresponding phenotypic differences between patients with *PRKAR1A* mutations and those without. This article summarizes the clinical manifestations of Carney complex from a worldwide collection of affected patients and also presents revised diagnostic criteria for Carney complex. In light of the recent identification of mutations in the *PRKAR1A* gene, an estimate of penetrance and recommendations for genetic screening are provided. (*J Clin Endocrinol Metab* 86: 4041–4046, 2001)

THE COMPLEX OF "spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas" or Carney complex (CNC) (1) (MIM 160980) (2) is an autosomal dominant, multiple neoplasia syndrome (3) that was initially described in 1985 under the rubric "the complex of myxomas, spotty pigmentation, and endocrine overactivity" (4). Isolated patients with some components of the complex, in particular cardiac myxomas and pigmentary anomalies, had previously been described under the acronyms NAME (nevi, atrial myxomas, and ephelides) and LAMB (lentigines, atrial myxomas, and blue nevi) (5, 6). Today, it is accepted that most, if not all, of these patients had CNC (7).

CNC may be viewed as a form of multiple endocrine neoplasia (8, 9) because affected patients often have tumors of two or more endocrine glands, including primary pigmented nodular adrenocortical disease (PPNAD), GH- and PRL-producing pituitary adenoma, testicular neoplasms [primarily large-cell calcifying Sertoli cell tumor (LCCSCT)], thyroid adenoma or carcinoma, and ovarian cysts (10–16). Additional unusual manifestations include psammomatous melanotic schwannoma (PMS), breast ductal adenoma, and, a rare bone tumor, osteochondromyxoma (17–21).

Abbreviations: CNC, Carney complex; LOH, loss of heterozygosity; LCCSCT, large-cell calcifying Sertoli cell tumor; MRI, magnetic resonance imaging; oGTT, oral glucose tolerance test; PMS, psammomatous melanotic schwannoma; PPNAD, primary pigmented nodular adrenocortical disease.

Epidemiology and inheritance of CNC

Three hundred thirty-eight patients with CNC are known: 144 (43%) males and 194 (57%) females, including Caucasians, African-Americans, and Asians from all continents [North and South America, Europe, Asia (Japan, China, India), Australia, and New Zealand]. Most of the patients (70%) belonged to 67 affected families, whereas 88 had no known affected relative. The genetic origin of the complex could not be definitively determined in 12 cases.

Previous estimates had indicated that approximately half of the cases of CNC were familial (1, 7, 22). The increased number of familial cases that we have observed reflects the application of a rigorous screening protocol for all first-degree relatives of affected patients (9). Careful history-taking often identified ancestors of an affected patient with cutaneous pigmented spots or obvious signs of endocrine disease. The detailed family data also demonstrated significant variability in clinical manifestations between patients, including members of the same family. This clinical variability was responsible for the apparent "skip" of a gener-

ation in extended CNC pedigrees and renders designation of a case as "sporadic" doubtful, unless careful clinical, imaging, and biochemical screening of all first-degree relatives has been obtained.

Transmission of CNC occurred through a female affected parent in 43 cases and from a male in only 9 cases. This excess of female transmission in an autosomal dominant syndrome (3) has been noted previously (23). CNC may have non-Mendelian features in some aspects of its inheritance (23), not unlike MEN 2 (24) and perhaps other familial cancer syndromes. However, LCCSCT, a frequent component of CNC in male patients (15), causes replacement and obstruction of seminiferous tubules and may also impair fertility by inappropriate hormone production or aromatization. In addition, several patients with CNC had undergone bilateral orchiectomy for LCCSCT (15, 25).

Although there were many families with CNC, the number of affected members in the majority of these was small. The maximum number of affected generations in a family was 5 (26). The small size of most CNC families precludes the use of genetic linkage studies in counseling kindreds that do not have *PRKAR1A* mutations (see below).

Age at detection of the first component

CNC is a developmental disorder. Diagnosis of the disease was made at birth in at least five patients. The median age at detection among 235 cases was 20 yr.

Although abnormal skin pigmentation may be present at birth, the characteristic skin changes, lentigines, usually do not assume their characteristic distribution, density, and intensity until the peripubertal period. Unlike other pigmented lesions affecting the aging skin, lentigines associated with CNC tend to fade after the fourth decade of life, but may be appreciable as late as the eighth decade.

Other pigmented lesions, including blue and other nevi, café-au-lait spots, and depigmented lesions may also be present at birth and referred to as "birthmarks"; more commonly, however, these lesions develop in the early childhood years. The café-au-lait spots in CNC are usually smaller and less pigmented than those in McCune-Albright syndrome. They also tend to fade with time. Their shape is reminiscent of those associated with the neurofibromatosis (NF) syndromes; however, unlike those of NF, café-au-lait spots in CNC do not usually enlarge with time.

During infancy, cardiac and cutaneous myxomas, and PPNAD are the most common tumors encountered. LCCSCT and thyroid nodules (appearing as microcalcifications and multiple, small, hypoechoic lesions on testicular and thyroid ultrasonography, respectively) often appear within the first 10 yr of life. The earliest detection of LCCSCT (by ultrasonography) was made in a 2-yr-old boy.

There seems to be a bimodal age distribution of PPNAD among CNC patients, a minority present during the first 2–3 yr, whereas the majority manifest in the second and third decade of life. Acromegaly usually is observed during the third and fourth decade of life. Gigantism is rare, as in the case of other familial forms of acromegaly (27). In contrast, cardiac myxomas are fairly equally distributed among the ages.

TABLE 1. Clinical manifestations of CNC *at the time of presentation* among 338 patients

Manifestation	No. of patients	Percentage
Spotty skin pigmentation	262	77
Heart myxoma	178	53
Skin myxoma	110	33
PPNAD	88	26
LCCSCT	42	33 (of male patients)
Acromegaly	33	10
PMS	33	10
Thyroid nodules or cancer	11	5
Breast ductal adenoma	6	3 (of female patients)

Clinical manifestations of CNC: a global perspective

The major clinical manifestations of CNC (at the time of presentation) are listed in Table 1. As has already been mentioned, spotty skin pigmentation is the most common clinical manifestation of CNC (1, 8, 22), although it is not invariably present. Other pigmentary abnormalities in the patients in addition to those already mentioned included usual and epithelioid-type blue nevi, combined nevi, and depigmented lesions.

Heart myxomas occurred at a young age (by comparison with the nonsyndromic tumor), multicentrically, and in any, or all, cardiac chambers. Fifty-one patients had two or more operations for recurrent tumor. Classic sites for skin myxomas included the eyelid, external ear canal, and nipple. Breast myxomas, often bilateral, were present in 34 female and 2 male patients. Other sites for myxomas were the oropharynx (tongue, 3; hard palate, 3; pharynx, 2), the female genital tract (uterus, 2; cervix, 1; vagina, 1), and the female pelvis (1).

Among the endocrine tumors, PPNAD was the most frequent manifestation of the disease, occurring in about one quarter of the patients. This number, however, significantly underestimates the true incidence of PPNAD among patients with CNC: biochemical screening by a dexamethasone-stimulation test has been shown to detect additional patients with PPNAD-associated subclinical, atypical, or periodic Cushing's syndrome, as suggested by Stratakis *et al.* (10). Furthermore, histologic evidence of PPNAD has been found in almost every patient with the complex who underwent an autopsy.

Another very common tumor was LCCSCT, which was often multicentric and bilateral. Again, the number presented in Table 1 is a major underestimate of the true incidence of this tumor among patients with CNC: ultrasonography identified testicular microcalcifications in most examined affected adult patients with CNC (15). Thus, LCCSCT is very prevalent and ultrasonography is an effective and inexpensive screening technique for its detection. LCCSCT is almost always benign (28); metastasis of the tumor has occurred in a 62-yr-old patient (28a). Testicular ultrasonography has also detected other tumors in CNC patients, including Leydig cell (two patients) and (pigmented nodular) adrenocortical rest tumors (three patients). In all the latter patients, LCCSCT was also present; one patient had all three testicular tumors. LCCSCT in CNC, as in Peutz-Jeghers syndrome, may be hormone producing; it has caused gynecomastia in prepubertal and peripubertal boys (five pa-

tients in our series) due to increased P-450 aromatase expression (25). The gynecomastia, unlike that due to familial aromatase excess, in which medical treatment with inhibitors of aromatization seems to be effective (29), usually requires orchiectomy to avoid premature epiphyseal fusion and induction of central precocious puberty.

Clinically evident acromegaly is a relatively infrequent manifestation of CNC. However, asymptomatic elevation of GH and IGF-I levels, as well as subtle hyperprolactinemia, may be present in up to 75% of the patients (11–13). Biochemical acromegaly is often unmasked by abnormal results of oral glucose tolerance test (oGTT) or paradoxical responses to TRH administration. Somatomammotroph hyperplasia, a putative precursor of GH-producing adenoma, may explain the insidious and protracted period of establishment of clinical acromegaly in CNC patients (13).

Up to 75% of patients with CNC may have multiple thyroid nodules, detected as small, hypoechoic lesions on ultrasonography (14). In our series of patients, most of these nodules were follicular adenomas, which were confirmed histologically in six patients (hyperfunctioning in two). Five thyroid carcinomas occurred among CNC patients, three papillary and two follicular, including one that developed in a patient with a long history of multiple adenomas (14, 30, 31). Thyroid ultrasonography is recommended as a satisfactory, cost-effective method for determining thyroid involvement in pediatric and young adult patients with CNC (9, 14); its value, however, is questionable in older patients.

PMS, a very rare tumor, occurred in 33 patients (17, 18). In six patients, the tumor was malignant. PMS may occur anywhere in the peripheral nervous system, but it is most frequently found in the gastrointestinal tract (esophagus and stomach) and paraspinal sympathetic chain. CNC is the only genetic condition other than the NF syndromes and isolated familial schwannomatosis that includes schwannomas. The particular schwannoma in CNC is distinctive because of its heavy pigmentation (melanin), frequent calcification, and multicentricity (18). If there are symptoms suggestive of this tumor, imaging of the spine, chest, abdomen (in particular the retroperitoneum), and the pelvis may be necessary for its detection.

Breast ductal adenoma, an unusual mammary tumor akin to intraductal papilloma, was detected in six women with CNC, and it was bilateral in three (19, 20). Other conditions probably associated with CNC are presented in Table 2; among them, only osteochondromyxoma of the bone (21) is, at present, considered a candidate component of the disorder. Parotid mixed tumor, marfanoid habitus, bronchogenic cyst, and hepatocellular adenoma, each occurred in one patient and are thought unlikely to be related to CNC. Finally, congenital heart disease, tetralogy of Fallot, in particular, has been observed in a number of families with CNC, although none of these patients had been screened for other manifestations of CNC; DNA from these patients is not available for molecular testing, but the association appears likely.

TABLE 2. Other conditions probably or possibly associated with CNC among 338 affected patients

Manifestation	No. of patients	Percentage
Osteochondromyxoma	6	2
Pilonidal sinus	9	3
Carcinoma or sarcoma[a]	8	2
Cardiomyopathy	3	1

[a] Colonic (rectum) (1), ovarian (2), mammary (1), gastric (1), and pancreatic (2) carcinomas and retroperitoneal malignant fibrous histiocytoma (1).

Mortality among CNC patients

Life span was decreased in patients with CNC. Fifty-one patients in the series (15%) are deceased, 29 due to heart-related causes (57% of the deaths). Table 3 presents a comprehensive list of causes of death in our series.

Molecular genetics of CNC

An initial linkage study of families with CNC demonstrated a genetic locus on 2p16 with an aggregate logarithm of odds score of 5.97 ($\theta = 0.03$), although no single family had a logarithm of odds score greater than 1.8 for the locus (22). Additional genetic studies uncovered families, in whom CNC did not segregate with 2p16 markers (32, 33). A genome-wide screen among the latter demonstrated linkage to a locus on 17q22–24 (26).

Most recently, two independent groups identified mutations of the *PRKAR1A* gene on 17q in CNC families that mapped to 17q22–24 and in several sporadic cases (34, 35). This gene encodes the type 1α regulatory subunit of PKA, which is known to be an important effector molecule in many endocrine signaling pathways (36). On screening a large cohort of 53 CNC kindreds collected over the past 20 yr at the NIH (Bethesda, MD) and the Mayo Clinic (Rochester, MN), mutations of *PRKAR1A* were identified in 15 of 34 families (44%), as well as 7 of 20 sporadic cases (35%), for an overall mutation rate of 40.7% (37) (Fig. 1).

PRKAR1A seems to function as a classic tumor suppressor gene in tumors from CNC patients (*i.e.* mutations of this gene are associated with loss of the normal allele), as shown by loss of heterozygosity (LOH) studies, in lesions caused by

TABLE 3. Causes of death among 51 patients with CNC

Cause	No. of patients	Percentage
Heart and heart-related	29	57
Cardiac myxoma	13	25
Cardiac myxoma emboli	6	12
Heart surgery complications	5	10
Cardiomyopathy	2	4
Probable cardiac arrhythmia	3	6
Psammomatous melanotic schwannoma	7	14
Metastatic PMS	6	12
Intracranial PMS	1	2
Postoperative complications (other than open heart surgery)	6	12
Bilateral adrenalectomy	2	4
Hernia	1	2
Abdominal emergency	2	4
Bilateral oophorectomy	1	2
Carcinoma or other metastatic tumor	7	14
Pancreas	2	4
Other abdominal tumor	3	6
Breast	1	2
Metastatic LCCSCT	1	2
Other/unknown	2	4

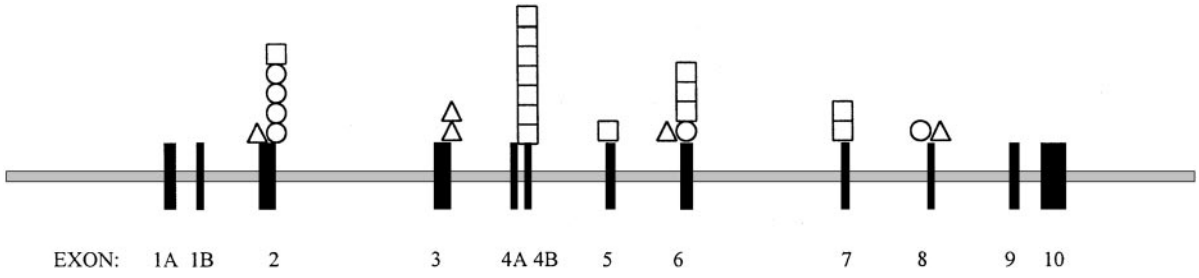

FIG. 1. Gene structure and location of mutations in *PRKAR1A* in patients with CNC. The structure of the *PRKAR1A* gene is shown, with the locations of the exons as indicated. Each *symbol* represents one family unit (kindred or sporadic case) with a mutation in that location. ○, Nonsense mutations; □, frameshifts △, splice site mutations. Each of the mutations in exon 4B represents the same 2-bp deletion. One of the exon 2 nonsense mutations and the exon 3 splice site mutation are seen in two kindreds each, whereas all other mutations are unique. (Data are from Refs. 34, 35, and 37.)

CNC (34). Indeed, LOH was essential in one group's identification of *PRKAR1A* as the causative gene in 17q-linked families (34). Subsequent studies, however, have shown that demonstrating LOH can often be hard due to significant admixture with normal cells in the mostly benign, hyperplastic tissue that either surrounds tumors (as is the case in the pituitary and adrenal glands) or is the primary lesion in CNC (C. A. Stratakis, unpublished data). Microdissection studies will be useful to study the exact stage of cellular development at which LOH occurs in lesions associated with the syndrome.

Each of the *PRKAR1A* mutations reported to date (Fig. 1) is predicted to lead to the production of a truncated protein product, so it is possible that the mutations could act by either haploinsufficiency (loss of function) or by a dominant negative effect (gain of function). To address this question, protein lysates from CNC cells examined by Western blotting have shown that foreshortened forms of the PRKAR1A protein are not produced (34, 37). Furthermore, analysis of mRNA in these cells has demonstrated selective degradation of the mutant messages, a phenomenon known as nonsense-mediated mRNA decay (37). Thus, both at the protein and mRNA levels, mutant *PRKAR1A* alleles have been demonstrated to be functionally null, indicating that constitutional (germ line) loss of one allele of *PRKAR1A* is the key factor in the pathogenesis of the disease. In CNC tumors, this loss of the PRKAR1A protein leads to enhanced intracellular signaling by PKA, as evidenced by an almost 2-fold greater response to cAMP in CNC tumors when compared with non-CNC tumors (34).

Because all of the chromosome 17 CNC alleles are functionally equivalent to null alleles, one would predict a lack of a genotype-phenotype correlation in patients with mutations of *PRKAR1A*. Indeed, this hypothesis is borne out by clinical study of the NIH-Mayo Clinic cohort of patients. Additionally, no significant differences have been identified between CNC patients that carry null mutations of *PRKAR1A* and those that do not (Stratakis, C. A., and L. S. Kirschner, unpublished observations). Thus, genetic, but not clinical, heterogeneity has been demonstrated in CNC (37, 38).

Penetrance of CNC

Because of the known genetic heterogeneity in CNC, and for the purposes of genetic counseling, it has been essential to use uniform criteria for the diagnosis of the disease. Preliminary diagnostic criteria were established for the initial clinical and genetic studies of Stratakis *et al.* (9, 22); these criteria were refined during an international meeting at the NIH in 1998 (39). The subsequent 3 yr have witnessed major additions to clinical and molecular knowledge of CNC.

TABLE 4. Diagnostic criteria for CNC[a]

1. Spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)
2. Myxoma (cutaneous and mucosal)[b]
3. Cardiac myxoma[b]
4. Breast myxomatosis[b] or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis[c]
5. PPNAD[b] or paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle's test[d]
6. Acromegaly due to GH-producing adenoma[b]
7. LCCSCT[b] or characteristic calcification on testicular ultrasonography
8. Thyroid carcinoma[b] or multiple, hypoechoic nodules on thyroid ultrasonography, in a young patient
9. Psammomatous melanotic schwannoma[b]
10. Blue nevus, epithelioid blue nevus (multiple)[b]
11. Breast ductal adenoma (multiple)[b]
12. Osteochondromyxoma[b]

Supplemental criteria:

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

[a] **To make a diagnosis of CNC, a patient must either: 1) exhibit two of the manifestations of the disease listed, or 2) exhibit one of these manifestations and meet one of the supplemental criteria (an affected first-degree relative or an inactivating mutation of the PRKAR1A gene).**

[b] With histologic confirmation.

[c] See Ref. 40.

[d] See Ref. 10.

TABLE 5. Findings suggestive or possibly associated with CNC, but not diagnostic for the disease

1.	Intense freckling (without darkly pigmented spots or typical distribution)
2.	Blue nevus, usual type (if multiple)
3.	Café-au-lait spots or other "birthmarks"
4.	Elevated IGF-I levels, abnormal oGTT, or paradoxical GH responses 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 and other skin lesions; lipomas
9.	Colonic polyps (usually in association with acromegaly)
10.	Hyperprolactinemia (usually mild and almost always in association with clinical or subclinical acromegaly)
11.	Single, benign thyroid nodule in a young patient; multiple thyroid nodules in an older patient (detected by ultrasonography)
12.	Family history of carcinoma, in particular of the thyroid, colon, pancreas and the ovary; other multiple benign or malignant tumors

The recent identification of the *PRKAR1A* gene defects in approximately 40% of CNC kindreds (37) has provided for the first time a means of estimating true penetrance of the disease in *PRKAR1A* mutation carriers, based on the diagnostic criteria previously suggested (9, 22). Among 48 subjects with inactivating mutations of the *PRKAR1A* gene, only one did not fully meet these criteria (2%). Thus, penetrance for CNC due to *PRKAR1A* defects seems to be close to 100%. However, because more than half of the examined kindreds did not harbor *PRKAR1A* mutations, it cannot be assumed that this estimate of penetrance applies to kindreds with CNC caused by other genetic defects.

Summary: diagnostic criteria for CNC and recommendations for screening and follow-up

The diagnostic criteria for CNC are provided in Table 4. These have been modified from those previously suggested (9, 22) by inclusion of imaging and biochemical screening and molecular testing procedures.

In brief, a patient is considered to have CNC if two major criteria are present; alternatively, the diagnosis may be made if one major criterion is present and a first-degree relative has CNC or an inactivating *PRKAR1A* mutation. At present, there is insufficient information about the value of the criteria listed in Table 5. Their presence may be considered suggestive of the disease and should stimulate careful patient and family history-taking and, possibly, further clinical, imaging, and laboratory studies.

For postpubertal pediatric patients and for adult patients of both sexes with established CNC, we recommend the following annual studies: echocardiogram, measurement of urinary free cortisol levels (which may be supplemented by diurnal cortisol or the overnight 1 mg dexamethasone testing) and serum IGF-I levels. Male patients should also have testicular ultrasonography at the initial evaluation; minute calcifications, presumably LCCSCT, may be followed by annual ultrasound thereafter. Thyroid ultrasonography should be obtained at the initial evaluation, and may be repeated as needed. Transabdominal pelvic ultrasonography in female patients is recommended during the first evaluation but need not be repeated, unless there is a detectable abnormality, because of the low risk of ovarian malignancy (16). Breast imaging may be required for the detection of breast tumors (40).

More elaborate clinical and imaging studies may be necessary for the detection of PPNAD and GH-producing pituitary adenoma in patients without overt clinical manifestations of adrenal or pituitary disease, respectively. For the former, a dexamethasone-stimulation test is recommended, performed, and interpreted with the diagnostic criteria suggested by Stratakis *et al.* (10). Diurnal cortisol levels ("short" diurnal variation test: insertion of an indwelling venous catheter to a hospitalized patient, followed by sampling for cortisol levels at 2330 h and 2400 h for the nighttime sample, and at 0730 h and 0800 h for the morning sample), in addition to adrenal computed tomography, may also be obtained. For the detection of early acromegaly, oGTT and TRH testing may be obtained in addition to IGF-I levels and pituitary MRI. IGF-I, oGTT, or TRH testing may be abnormal in patients with CNC several years before a pituitary tumor is visible on MRI (if one is ever detected) (13).

Pediatric patients with CNC should have echocardiography during the first 6 months of life and annually thereafter; biannual echocardiographic evaluation may be necessary for pediatric patients with history of an excised myxoma. Most endocrine tumors in CNC do not become clinically significant until the second decade in life (although they might be detectable at a much earlier age) and imaging or biochemical screening in young, prepubertal children are not considered necessary, except for diagnostic purposes. However, pediatric patients with LCCSCT (or a microcalcification upon testicular ultrasonography) need close monitoring of growth rate and pubertal status; some may require bone age determination and further laboratory evaluation, especially if gynecomastia is present.

Conclusions

Clinical and biochemical screening for CNC remains the gold standard for the diagnosis of CNC. Testing for *PRKAR1A* mutations is not recommended at present for patients with CNC, but may be advised for detection of affected patients in families with known mutations of that gene to avoid unnecessary medical surveillance of noncarriers. Once the other gene(s) responsible for the disease is identified, DNA testing may become the most effective screening tool for patients suspected of having CNC. However, it is unlikely, that DNA testing will have 100% accuracy; this limitation suggests that molecular diagnosis will aid, but never replace, thorough clinical investigation.

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