GENEReviews

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Carney Complex

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[Familial Myxoma, Carney Syndrome]

Summary

Disease characteristics. Carney complex (CNC) is characterized by skin pigmentary abnormalities, myxomas, endocrine tumors or overactivity, and schwannomas. Pale brown to black lentigines are the most common presenting feature of CNC and typically increase in number at puberty. Cardiac myxomas occur at a young age, may occur in any or all cardiac chambers, and manifest as intracardiac obstruction of blood flow, embolic phenomenona, and/or heart failure. Other sites for myxomas include the skin, breast, oropharynx, and female genital tract. Primary pigmented nodular adrenocortical disease (PPNAD) causing Cushing syndrome, the most frequent endocrine tumor observed in CNC, occurs in approximately 25% of individuals. Large-cell calcifying Sertoli cell tumors (LCCSCTs) are observed in one-third of affected males within the first decade and in almost all adult males. Up to 75% of individuals with CNC have multiple thyroid nodules, most of which are thyroid follicular adenomas. Clinically evident acromegaly from a growth hormone (GH)-producing adenoma is evident in approximately 10% of adults. Psammomatous melanotic schwannoma (PMS), a rare tumor of the nerve sheath, occurs in an estimated 10% of affected individuals. The median age of diagnosis is 20 years.

Diagnosis/testing. The diagnosis of CNC usually relies on clinical diagnostic criteria. Mutations in two genes, *PRKAR1A* and an unknown gene at chromosomal locus 2p16, are causative. Sequence analysis of the *PRKAR1A* coding region, available on a clinical basis, has a mutation detection rate of approximately 55%.

Management. *Treatment of manifestations:* open-heart surgery for cardiac myxomas; surgical excision of cutaneous and mammary myxoma; bilateral adrenolectomy for Cushing syndrome; transsphenoidal surgery for pituitary adenoma; surgery for cancerous thyroid adenomas; orchiectomy for boys with LCCSCT and gynecomastia to avoid premature epiphyseal fusion and induction of central precocious puberty; surgery to remove primary and/or metastatic PMS. *Surveillance:* for prepubertal children: echocardiography during the first six months of life and annually thereafter; for boys with LCCSCT: close monitoring of linear growth rate and pubertal status; for postpubertal children and adults: annual echocardiogram, assessment of adrenal function, measurement of plasma insulin-like growth factor type-1 (IGF-1) concentration, and testicular ultrasound when minute calcifications are present; thyroid ultrasonography as needed; follow-up of breast ductal adenoma; clinical and imaging studies to detect PPNAD and GH-producing pituitary adenoma. *Testing of relatives at risk:* when the family-specific

mutation is known, molecular genetic testing to clarify the genetic status of at-risk family members so that appropriate evaluation and surveillance can enable early diagnosis of 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.

Diagnosis

Clinical Diagnosis

The diagnosis of Carney complex (CNC) is established in individuals who (1) have either two or more of the disease manifestations listed **or** (2) have one disease manifestation and also meet one of the supplemental criteria [Carney et al 1986; Carney & Young 1992; Carney 1995; Stratakis et al 1998; Kirschner, Carney et al 2000; Kirschner, Sandrini et al 2000; Stratakis 2000; Stratakis et al 2001].

Disease manifestations

- **Skin pigmentary abnormalities**
  - Multiple lentigines of the face, the vermilion border of the lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa
  - Blue nevus, epithelioid blue nevus (composed of intradermal melanin-laden large polygonal epithelioid melanocytes without dermal fibrosis)*
- **Myxoma**
  - Cutaneous myxoma (with predilection for the eyelid at the mucosal-epithelial junction, external ear canal, nipple, and external genitalia)
  - Cardiac myxoma (usually pedunculated friable gelatinous tumors arising from endocardial surfaces). The tumors are commonly multiple and may affect any or all chambers. Recurrence is frequent.
  - Breast myxomatosis (also evident in fat-suppressed MRI of the breast, in the absence of a biopsy)
  - Osteochondromyxoma of bone
- **Endocrine tumors/overactivity**
  - Primary pigmented nodular adrenocortical disease (PPNAD) (a micronodular form of adrenal hyperplasia)* **or** evidence of adenocortical overactivity demonstrated by a paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle's test, a test for Cushing syndrome, involving four days of administration of dexamethasone.

    Note: The diagnosis of PPNAD may be difficult to establish because the hypercortisolism may be periodic and adrenal nodules may not be detected by imaging studies.
  - Growth hormone (GH)-producing pituitary adenoma* or evidence of excess GH production or acromegaly

  - Large-cell calcifying Sertoli cell tumor (LCCSCT)* **or** characteristic microcalcification or hyperechoic lesions on testicular ultrasonography
  - Thyroid adenoma or carcinoma (papillary or follicular) **or** multiple, hypoechoic nodules on thyroid ultrasonography
- **Schwannoma.** Psammomatous melanotic schwannoma (PMS),* nerve sheath tumors (NSTs) characterized by heavy pigmentation (melanin), frequent calcification, and multicentricity
- **Other.** Breast ductal adenoma (multiple), an unusual mammary tumor similar to intraductal papilloma

*Histologically confirmed

Supplemental criteria

- Affected first-degree relative (i.e., parent, sibling, child)
- Inactivating mutation of the *PRKAR1A* gene

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. *PRKAR1A* is the only gene currently known to be associated with CNC [Schoenberg-Fejzo et al 1999; Stratakis et al 1999; Kirschner, Sandrini et al 2000].

Other loci

- Approximately 20% of families affected with CNC have been linked to 2p16 [Stratakis et al 1996].
- It is possible that a third as-yet unidentified locus exists.

Clinical testing

- **Sequence analysis.** Sequence analysis of the *PRKAR1A* coding region detected mutations in 111 of 202 (55%) affected families studied [Sandrini & Stratakis 2003, Boikos & Stratakis 2007].

Research testing

- **Deletion/duplication analysis.** In a study of 36 unrelated individuals with CNC who were negative for *PRKAR1A* point mutations, two large *PRKAR1A* deletions were identified [Horvath et al, in press].
- **Linkage analysis.** For those individuals without an identifiable *PRKAR1A* mutation, linkage analysis may be available on a research basis.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Carney Complex

Test Method	Mutations Detected	Mutation Detection Frequency by test method	Test Availability
Sequence analysis	*PRKAR1A* point mutations	55%	Clinical Testing
Deletion/duplication analysis	Large *PRKAR1A* mutations	~2%	Research only

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis in a proband. Molecular genetic testing of *PRKAR1A* involves bidirectional sequencing of all coding sequences and exon-intron junctions.

Predictive testing for young at-risk asymptomatic family members requires prior identification of the disease-causing mutation in the family.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

The following phenotypes are also associated with mutations in *PRKAR1A*:

- Sporadic isolated (not CNC-associated) PPNAD [Groussin et al 2002]
- Sporadic undifferentiated thyroid cancers and sporadic papillary thyroid cancers [Sandrini, Matyakhina et al 2002]
- Adrenal tumors [Bertherat et al 2003]

Odontogenic myxomas, which have never been seen in the context of CNC, have been associated with somatic *PRKAR1A* mutations [Perdigao et al 2005].

Clinical Description

Natural History

The Carney complex (CNC) of skin pigmentary abnormalities, myxomas, endocrine tumors or overactivity, and schwannomas may be evident at birth, although the median age of diagnosis is 20 years.

Skin pigment abnormalities

- Pale brown to black lentigines are the most common presenting feature of CNC and may be present at birth. Typically, they increase in number and appear anywhere on the body including the face, the lips, and mucosa around puberty. These lentigines tend to fade after the fourth decade, but may still be evident in the 70s.
- Additional pigmentary abnormalities that develop over time are epithelioid-type blue nevi (small bluish domed papules with a smooth surface), combined nevi, café au lait spots, and depigmented lesions.

Myxomas

- Cutaneous myxomas are papules or subcutaneous nodules that usually have a smooth surface and are white, flesh-colored, opalescent, or pink. They appear between birth

and the fourth decade. Most individuals with CNC have multiple lesions. Myxomas occur on any part of the body except the hands and feet and typically affect the eyelids, external ear canal, and nipples.

- Cardiac myxomas occur at a young age and may occur in any or all cardiac chambers. Cardiac myxomas present with symptoms related to intracardiac obstruction of blood flow, embolic phenomenona (into the systemic circulation), and/or heart failure. Myxomas that completely occlude a valvular orifice can cause sudden death.
- Breast myxomas, often bilateral, occur in females after puberty. Both males and females may develop breast nipple myxomas at any age.
- Other sites for myxomas include the oropharynx (tongue, hard palate, pharynx) and the female genital tract (uterus, cervix, vagina).
- Osteochondromyxoma is a rare myxomatous tumor of the bone that affects nasal sinuses and long bones.

Endocrine tumors

- **Primary pigmented nodular adrenocortical disease (PPNAD)** is associated with adrenocorticotropic hormone (ACTH)-independent overproduction of cortisol (hypercortisolism). PPNAD is the most frequently observed endocrine tumor in individuals with CNC, occurring in an estimated 25% of affected individuals. Histologic evidence of PPNAD has been found in almost every individual with CNC undergoing autopsy. Symptomatic individuals have Cushing syndrome. The hypercortisolism of PPNAD is usually insidious in onset. In children, hypercortisolism is manifest first as weight gain and growth arrest. In adults, longstanding hypercortisolism results in central obesity, "moon facies," hirsutism, striae, hypertension, buffalo hump fat distribution, weakness, easy bruising, and psychological disturbance. In a minority of individuals, PPNAD presents in the first two to three years; in the majority it presents in the second and third decade.
- **GH-producing adenoma.** Clinically evident acromegaly is a relatively frequent manifestation of CNC, occurring in approximately 10% of adults at the time of presentation. Gigantism, resulting from excess GH secretion prior to puberty, is rare. However, asymptomatic increased serum concentration of GH and insulin-like growth factor type-1 (IGF-1) — as well as subtle hyperprolactinemia — may be present in up to 75% of individuals with CNC. Somatomammotroph hyperplasia, a putative precursor of GH-producing adenoma, may explain the protracted period of onset of clinical acromegaly in individuals with CNC.
- **Testicular tumors.** Large-cell calcifying Sertoli cell tumors (LCCSCT) are observed in one-third of affected males at the time of presentation, which is often within the first decade. Most adult males with CNC have evidence of LCCSCT. The tumors are often multicentric and bilateral. LCCSCT is almost always benign; malignancy has been reported only once, in a 62-year-old. LCCSCT may be hormone producing; gynecomastia in prepubertal and peripubertal boys may result from increased P-450 aromatase expression. Other testicular tumors observed in individuals with LCCSCT include Leydig cell tumors and (pigmented nodular) adrenocortical rest tumors.
- **Thyroid adenoma or carcinoma.** Up to 75% of individuals with CNC have multiple thyroid nodules, most of which are nonfunctioning thyroid follicular adenomas. Thyroid carcinomas, both papillary and follicular, can occur and occasionally may develop in a person with a long history of multiple thyroid adenomas.

Schwannomas

- **Psammomatous melanotic schwannoma (PMS).** This rare tumor of the nerve sheath occurs in approximately 10% of individuals with CNC. Malignant degeneration occurs in approximtely 10% of those with CNC [Watson et al 2000]. PMS may occur anywhere in the central and peripheral nervous system; it is most frequently found in the nerves of the gastrointestinal tract (esophagus and stomach) and paraspinal sympathetic chain (28%). The spinal tumors present as pain and radiculopathy in adults (mean age 32 years).

Other

- **Breast ductal adenoma.** Breast ductal anenoma is a benign tumor of the mammary gland ducts.

Age at presentation. CNC may present at any age; it most commonly presents in the teen years and early adulthood.

Life span. Most individuals with CNC have a normal life span. However, because some die at an early age, the average life expectancy for individuals with CNC is 50 years. Causes of death include complications of cardiac myxoma (myxoma emboli, cardiomyopathy, cardiac arrhythmia, surgical intervention), metastatic or intracranial PMS, thyroid carcinoma, and metastatic pancreatic and testicular tumors.

Fertility. LCCSCT causes replacement and obstruction of seminiferous tubules, macroorchidism, oligoasthenospermia, and inappropriate hormone production or aromatization.

Genotype-Phenotype Correlations

No statistically significant differences have been observed between individuals with CNC with and without a *PRKAR1A* mutation.

For most identified *PRKAR1A* mutations, no genotype-phenotype correlations have been seen. However, in a recent study one of the most commonly observed mutations, c. 709-2_709-7delATTTTT, was associated with a very mild, mostly adrenal phenotype [Groussin et al 2006].

Penetrance

Penetrance is 70%-80% by age 40 years.

Nomenclature

Carney complex has also been designated by the following names:

- NAME: **n**evi, **a**trial **m**yxomas, **e**phelides
- LAMB: **l**entigines, **a**trial **m**yxoma, **b**lue nevi

"Carney triad" is a completely different entity consisting of a triad of gastric leiomyosarcoma, pulmonary chondroma, and extra-adrenal paraganglioma.

Prevalence

More than 600 individuals with CNC are known to the authors. These include Caucasians, African Americans, and Asians, from North and South America, Europe, Australia, and Asia.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Skin. Disorders in which lentigines occur include benign familial lentiginosis, Peutz-Jeghers syndrome, LEOPARD syndrome, Noonan syndrome with lentiginosis, and the Bannayan-Riley-Ruvalcaba syndrome which is one of the phenotypes observed in the *PTEN* hamartoma tumor syndrome. The café au lait spots of Carney complex (CNC) can resemble those of McCune-Albright syndrome, neurofibromatosis type 1, neurofibromatosis type 2, and Watson syndrome. Epithelioid blue nevi may occur as solitary lesions in individuals who have no findings to suggest CNC.

Cardiac myxoma. Cardiac myxoma is the most common type of cardiac tumor in adults and accounts for approximately 30% of cardiac tumors in children. Genetic studies reveal no apparent association between CNC and sporadic myxomas [Fogt et al 2002].

Kindreds have been described with familial myxomas, CNC, and cardiomyopathy associated with a single mutation of a protein that belongs to the family of myosins [Veugelers et al 2004]. This condition is distinct from CNC and is either a separate disorder or the concurrence of two genetic disorders in one family [Stratakis et al 2004].

Endocrine tumors. Thyroid tumors also occur in Cowden syndrome, one of the phenotypes observed in the *PTEN* hamartoma tumor syndrome. Rarely, sporadic thyroid tumors may harbor somatic *PRKAR1A* mutations [Sandrini, Matyakhina et al 2002].

Large-cell calcifying Sertoli cell tumor (LCCSCT) is also seen in Peutz-Jeghers syndrome, in which the tumor may also be hormone producing. Ovarian tumors similar to those seen in Peutz-Jeghers syndrome are not observed in CNC [Stratakis, Papageorgiu et al 2000].

CNC accounts for approximately 80% of bilateral micronodular adrenal hyperplasia; sporadic isolated (not CNC-associated) primary pigmented nodular adrenocortical disease (PPNAD) can also be caused by mutations in *PRKAR1A* [Groussin et al 2002]. Isolated micronodular adrenocortical hyperplasia may be associated with inactivating mutations in the *PDE11A*, the gene encoding dual-specificity phosphodiesterase [Horvath et al 2006].

Adrenal cortical tumors are also seen in Beckwith-Wiedemann syndrome, Li-Fraumeni syndrome, multiple endocrine neoplasia type 1, congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency, and the McCune-Albright syndrome [Kjellman et al 2001].

GH-secreting pituitary adenomas (somatotropinomas) can also be seen in multiple endocrine neoplasia type 1 (MEN1) or isolated familial somatotropinomas (IFS), which maps to 11q13.1-q13.3 or 2p16 [Stratakis & Kirschner 2000, Frohman 2003]. Sporadic somatotropinomas or non-CNC- and non-MEN1-associated somatotropinomas do not appear to be frequently associated with *PRKAR1A* mutations [Sandrini, Kirschner et al 2002; Yamasaki et al 2003].

Schwannomas. CNC is the only genetic condition other than neurofibromatosis type 1, neurofibromatosis type 2, and isolated familial schwannomatosis in which schwannomas occur.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Carney complex (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. The test need not be repeated because of the low risk of ovarian malignancy unless an abnormality is detected initially.

Treatment of Manifestations

The following interventions are routine:

- **Cardiac myxoma.** Open-heart surgery
- **Cutaneous and mammary myxoma.** Surgical excision
- **Cushing syndrome.** Bilateral adrenolectomy
- **Pituitary adenoma.** Transsphenoidal surgery
- **Thyroid andenomas.** Surgery if cancerous
- **LCCSCT.** Orchiectomy usually required for boys with LCCSCT and gynecomastia to avoid premature epiphyseal fusion and induction of central precocious puberty
- **PMS.** Surgery to remove primary and/or metastatic lesions

Surveillance

The following are recommended for prepubertal children:

- Echocardiography during the first six months of life and annually thereafter; closer follow-up may be necessary for children following excision of a cardiac myxoma.
- Children with LCCSCT (or microcalcifications observed on testicular ultrasonography) need close monitoring of linear growth rate and pubertal status; some may require bone age determination and further laboratory evaluation for possible aromatase excess resulting in increased estrogen levels.

The following are recommended for postpubertal children and adults of both sexes with established CNC:

- Annual echocardiogram
- Annual measurement of urinary free cortisol concentration (which may be supplemented by diurnal measurement of serum cortisol concentration) or the overnight 1-mg dexamethasone testing
- Annual measurement of plasma IGF-1 concentration
- Thyroid ultrasonography repeated as needed

- Minute testicular calcifications, presumably a manifestation of LCCSCT, may be followed by annual ultrasonography thereafter.
- Clinical follow-up of breast ductal adenoma

More elaborate clinical studies and imaging studies may be necessary for the detection of PPNAD and GH-producing pituitary adenoma in those without overt clinical manifestations of adrenal or pituitary disease.

- For PPNAD, a dexamethasone-stimulation test is recommended [Casey et al 1998] in addition to adrenal computed tomography (CT) to detect PPNAD-associated subclinical, atypical, or periodic Cushing syndrome. Diurnal plasma cortisol concentrations may also be obtained.
- For the early detection of a GH-producing pituitary adenoma, oral glucose tolerance (OGT) and thyrotrophin-releasing hormone (TRH) testing may be obtained in addition to plasma IGF-1 concentration and pituitary MRI.

If findings suggestive of PMS are present, imaging of the brain, spine, chest, abdomen (in particular the retroperitoneum), and the pelvis may be necessary.

Testing of Relatives at Risk

When a clinically diagnosed relative has undergone molecular genetic testing and is found to have a mutation in *PRKAR1A*, 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 of CNC (see Evaluations Following Initial Diagnosis and Surveillance).

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Carney complex (CNC) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 70% of individuals diagnosed with CNC have an affected parent.
- Approximately 30% of individuals have CNC as the result of a *de novo* mutation.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include eliciting pertinent family history, physical examination for evidence of cutaneous pigmented spots or lumps or both and for signs of endocrine disease, and imaging and/or biochemical screening. If a mutation in *PRKAR1A* has been identified in the proband, molecular genetic testing of the parents should be considered.

Note: Although most individuals diagnosed with CNC have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members or early death of the parent before the onset of symptoms.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- In the absence of known family history, the risk to sibs of the proband is approximately 1%.
- Germline mosaicism has not been observed in individuals with CNC.

Offspring of a proband

- Each child of an individual with CNC has a 50% chance of inheriting the mutation.
- Fertility may be impaired in males with CNC.
- It is possible that pregnancies in which a *PRKAR1A*-inactivating mutation is present are more likely to end in spontaneous abortion; however, no data are yet available.

Other family members of a proband. The risk to the other family members depends on the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

See Management, Testing of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Testing at-risk asymptomatic adults and children. Consideration of molecular genetic testing of young at-risk family members is appropriate for guiding medical management (see Management).

When a clinically diagnosed relative has undergone molecular genetic testing and is found to have a mutation in *PRKAR1A*, molecular genetic testing can be used with certainty to clarify the genetic status of at-risk family members.

When a clinically diagnosed relative is not available for testing, the use of molecular genetic testing for determining the genetic status of at-risk relatives is problematic, and test results need to be interpreted with caution.

- A positive test result in an at-risk family member indicates (1) that the family member has a *PRKAR1A* disease-causing mutation and (2) that the same molecular genetic testing method can be used to assess the genetic status of other at-risk family members.
- Failure to identify a disease-causing mutation in an at-risk family member does not eliminate the possibility that a *PRKAR1A* disease-causing mutation is present; such individuals need to follow the recommendations for clinical surveillance of at-risk family members.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Molecular genetic testing. Prenatal testing for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele in the family must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Fetal ultrasound examination. A fetal heart tumor detected prenatally by ultrasound examination in an at-risk fetus may suggest the diagnosis; however, absence of such prenatal ultrasound findings does not rule out the diagnosis.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Carney Complex

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
CNC1	*PRKAR1A*	17q23-q24	cAMP-dependent protein kinase type I-alpha regulatory subunit
CNC2	Unknown	2p16	Unknown

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Carney Complex

160980	CARNEY COMPLEX, TYPE 1; CNC1
188830	PROTEIN KINASE, cAMP-DEPENDENT, REGULATORY, TYPE I, ALPHA; PRKAR1A
605244	CARNEY COMPLEX, TYPE II; CNC2

Table C. Genomic Databases for Carney Complex

Locus Name	Gene Symbol	Entrez Gene	HGMD
CNC1	*PRKAR1A*	5573 (MIM No. 188830)	PRKAR1A
CNC2	Unknown	1257 (MIM No. 605244)	

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

PRKAR1A appears to function as a classic tumor suppressor gene in tumors from individuals with Carney complex (CNC) as demonstrated in loss of heterozygosity (LOH) studies. Indeed, LOH was essential in identifying *PRKAR1A* as the causative gene in the families mapping to 17q22-24 [Kirschner, Carney et al 2000]. Subsequent studies, however, have shown that demonstrating LOH can be difficult because of significant admixture of tumor cells with normal cells in the mostly benign, hyperplastic tissue that either surrounds tumors (as is the case in the pituitary and adrenal glands) or in the primary lesion in CNC [Stratakis, unpublished data]. Microdissection studies to determine the exact stage of cellular development at which LOH occurs in lesions associated with the syndrome are in progress. In some tumors, however, LOH is not detected [Bertherat et al 2003, Tsilou et al 2004]. Recently, a mouse model of the disease was made available [Griffin et al 2004, Cancer Res]; LOH was not a consistent feature in the mouse tumors [Griffin et al 2004, J Med Genet].

Western blot testing of protein lysates from CNC cells demonstrated that foreshortened forms of the protein encoded for by *PRKAR1A* are not produced. In addition, analysis of mRNA in these cells has demonstrated selective degradation of mutant mRNA, a phenomenon known as nonsense-mediated mRNA decay. Thus, it has been demonstrated at both the protein and mRNA levels that these mutant alleles are functionally null, indicating that loss of one allele of *PRKAR1A* is key in disease pathogenesis. In CNC tumors, loss of the PRKAR1A protein leads to enhanced intracellular signaling by protein kinase A (PKA), as evidenced by an almost twofold greater response to cAMP in CNC tumors when compared to non-CNC tumors.

Normal allelic variants: *PRKAR1A* has 11 exons. See Table 2 for normal allelic variants.

Pathologic allelic variants: Mutations have been found in all ten exons. The following mutations of *PRKAR1A* have been described in individuals with Carney complex (see Table 2):

Table 2. *PRKAR1A* Allelic Variants Discussed in This *GeneReview*

Class of Variant Allele	DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change [2]	Number of Alleles	Reference
Normal	c.87G>A	p.(=)	--	Not reported
	c.204A>G	p.(=)	--	Not reported
	c.318G>C	p.(=)	--	Not reported
	c.349-5dupT (IVS3-5dupT)	--	--	Not reported
	c.892-43G>T (IVS9-34G>T)	--	--	Not reported
	c.973-102A>T (IVS10-102A>T)	--	--	Not reported
Pathologic	c.1A>G	p.Met1Val	9	Kirschner, Carney et al 2000
	c.82C>T	p.Gln28X	2	Kirschner, Sandrini et al 2000
	c.109C>T	p.Gln37X	1	Cazabat et al 2006
	c.124C>T	--	5	Kirschner, Sandrini et al 2000
	c.286C>T	p.Arg96X	8	Urban et al 2007
	c.682C>T	p.Arg227X	9	Kirschner, Sandrini et al 2000
	c.786_787delGGinsCT	p.Trp262CysfsX2	3	Kirschner, Sandrini et al 2000
	c.638C>A	p.Ala213Asp	8	Perdigao et al 2005
	c.85_95del11	p.Ala29ArgfsX12	1	Cazabat et al 2006
	c.101_105del5	p.Ser34CysfsX9	3	Kirschner, Sandrini et al 2000
	c.139delA	p.Met46TrpfsX82	1	Imai et al 2005
	c.491_492delTG	p.Val164ArgfsX5	38	Kirschner, Carney et al 2000
	c.530delTTAT	p.Val117fs26X	1	Kirschner, Carney et al 2000
	c.566_567delAAinsCAC	p.Glu188AlafsX44	3	Kirschner, Sandrini et al 2000
	c.693insT	p.Arg232X	1	Kirschner, Sandrini et al 2000
	c.712insAA	p.Ser238LysfsX4	2	Kirschner, Sandrini et al 2000
	c.846insA	p.Val282SerfsX9	1	Cazabat et al 2006
	c.178-2A>G	--	--	Kirschner, Sandrini et al 2000
	c.348+1G>C	--	--	Kirschner, Sandrini et al 2000

	c.550-2_550-9 delATTTCACG (c.550 (-9-2)del8)	--	--	Kirschner, Sandrini et al 2000
	c.708+1G>T	--	--	Kirschner, Sandrini et al 2000
	c.709-2_709-7 delATTTTT (c.709 (-7-2) del 6)	--	--	Groussin et al 2006
	c.891+3A>G	--	--	Kirschner, Sandrini et al 2000
	c.178_348del171	--	--	Horvath et al, in press

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

Reference sequences: NM_212472.1 and NP_997637.1 (GenBank)

1. Variant designation that does not conform to current naming conventions
2. The designation p.(=) means that the protein has not been analyzed, but no change is expected (Human Genome Variation Society).

Normal gene product: *PRKAR1A* encodes cAMP-dependent proteind kinase type I-alpha regulatory subunit (PRKAR1A), which has 381 amino acids and is an important effector molecule in many endocrine signaling pathways [Kirschner, Carney et al 2000; Kirschner, Sandrini et al 2000].

Abnormal gene product: Almost all mutations reported to date are predicted to lead to the production of a truncated protein product [Sandrini & Stratakis 2003], as the nonsense mRNA is degraded by nonsense mRNA-mediated decay (NMD) [Kirschner, Sandrini et al 2000]. Thus, most mutations completely inactivate PRKAR1A at the tissue level by NMD and LOH (see Molecular Genetic Pathogenesis. Rare mutations are expressed and do not undergo NMD; these do not appear to be associated with LOH and the mechanism of tumorigenesis remains unclear [Groussin et al 2002].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

American Cancer Society
Provides contact information for regional support.
1599 Clifton Road NE
Atlanta GA 30329
Phone: 800-227-2345
www.cancer.org

American Heart Association
National Center
7272 Greenville Avenue
Dallas TX 75231
Phone: 800-AHA-USA-1 (800-242-8721)
www.americanheart.org

Cancer Information Network
www.cancernetwork.com

National Cancer Institute (NCI)
www.nci.nih.gov

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

American Society of Clinical Oncology (2003) Statement on genetic testing for cancer susceptibility

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Chapter Notes

Unit on Genetics and Endocrinology Web site

Revision History

- 10 January 2008 (me) Comprehensive update posted to live Web site
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