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Carney Complex

Synonym: Carney Syndrome

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Summary

Clinical 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 can manifest as intracardiac obstruction of blood flow, embolic phenomenon, and/or heart failure. Other sites for myxomas include the skin, breast, oropharynx, and female genital tract. Primary pigmented nodular adrenocortical disease (PPNAD), which causes Cushing syndrome, is the most frequently observed endocrine tumor in CNC, occurring in approximately 25% of affected individuals. Large cell calcifying Sertoli cell tumors (LCCSCTs) are observed in one third of affected males within the first decade and in most adult males. Up to 75% of individuals with CNC have multiple thyroid nodules, most of which are nonfunctioning 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 clinical diagnosis of CNC is established in a proband with two or more major diagnostic criteria. The molecular diagnosis can be established in a proband with suggestive findings and a heterozygous germline pathogenic variant in *PRKAR1A* identified by molecular genetic testing.

Management

Treatment of manifestations: Surgical excision via open heart surgery for cardiac myxomas; surgical excision of cutaneous and mammary myxomas; bilateral adrenalectomy for Cushing syndrome; transsphenoidal surgery for pituitary adenoma; surgery for cancerous thyroid adenomas; orchiectomy for boys with aggressive LCCSCT and gynecomastia to avoid premature epiphyseal fusion and induction of central precocious puberty (mild

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gynecomastia may be treated medically); surgery to remove primary and/or metastatic PMS; standard treatment for pancreatic tumors.

Surveillance: Echocardiography annually beginning in childhood, biannually for those with a history of excised myxoma; clinical examination for cutaneous myxomas as needed; urinary free cortisol levels annually beginning in adolescence with diurnal cortisol levels, dexamethasome stimulation test, and adrenal CT as needed; annual serum IGF-1 beginning in adolescence, pituitary MRI, three-hour oral glucose tolerance test, and 90-minute thyrotropin-releasing hormone testing for those with gigantism/acromegaly; annual thyroid ultrasound beginning in adolescence; monitor growth rate and pubertal staging at each visit and testicular ultrasound annually in males beginning in childhood; transabdominal ultrasound of ovaries as needed in females; clinical assessment for PMS with MRI of the brain, spine, chest, abdomen, retroperitoneum, and pelvis as needed.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing of the *PRKAR1A* pathogenic variant in the family in order to identify as early as possible those who would benefit from initiation of surveillance and treatment. Surveillance is recommended for individuals at 50% risk when molecular genetic testing is not possible or is not informative.

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* pathogenic variant. Each child of an individual with CNC has a 50% chance of inheriting the pathogenic variant. Once the *PRKAR1A* pathogenic variant has been identified in an affected family member, predictive testing for at-risk family members and prenatal and preimplantation genetic testing are possible.

Diagnosis

Consensus clinical diagnostic criteria for Carney complex (CNC) have been published [Mateus et al 2008]. Criteria are reprinted with permission from Elsevier Publishing.

Suggestive Findings

CNC **should be suspected** in individuals with any of the following major diagnostic criteria with or without additional common findings.

Major diagnostic criteria

- Spotty skin pigmentation with typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)
- Myxoma * (cutaneous and mucosal)
- Cardiac myxoma *
- Breast myxomatosis * or fat-suppressed MRI findings suggestive of this diagnosis
- Primary pigmented nodular adrenocortical disease (PPNAD) * or paradoxic positive response of urinary glucocorticosteroid excretion to dexamethasone administration during Liddle's test
- Acromegaly as a result of growth hormone (GH)-producing adenoma *
- Large cell calcifying Sertoli cell tumor (LCCSCT) * or characteristic calcification on testicular ultrasound
- Thyroid carcinoma * or multiple, hypoechoic nodules on thyroid ultrasound in a child younger than age 18 years
- Psammomatous melanotic schwannoma (PMS) *
- Blue nevus, epithelioid blue nevus *
- Breast ductal adenoma *

- Osteochondromyxoma *
- **Family history** of CNC consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations)

Note: Criteria denoted by * are based on histologic confirmation.

Additional possible associations or symptoms

- Intense freckling (without darkly pigmented spots or typical distribution)
- Multiple blue nevi, common type
- Café au lait macules or other "birthmarks"
- Elevated insulin-like growth factor 1 (IGF-1) levels, abnormal glucose tolerance test (GTT), or paradoxic GH response to thyrotropin-releasing hormone (TRH) testing in the absence of clinical acromegaly
- Cardiomyopathy (due to cardiac myxoma)
- Multiple skin tags or other skin lesions; lipomas
- Colonic polyps (usually in association with acromegaly)
- Hyperprolactinemia (usually mild and almost always combined with clinical or subclinical acromegaly)
- Single, benign thyroid nodule in a child younger than age 18 years; multiple thyroid nodules in an individual older than age 18 years (detected on ultrasound examination)
- Family history of carcinoma, in particular of the thyroid, pancreas, and ovary; other multiple benign or malignant tumors; Cushing syndrome; acromegaly; or sudden death

Establishing the Diagnosis

The clinical diagnosis of CNC **is established** in a proband with two or more major diagnostic criteria (see Suggestive Findings), or the molecular diagnosis can be established in a proband with any suggestive findings and a heterozygous germline pathogenic (or likely pathogenic) variant in *PRKAR1A* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of a heterozygous *PRKAR1A* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *PRKAR1A* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

- **A multigene panel** that includes *PRKAR1A* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Carney Complex

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
PRKAR1A	Sequence analysis [3]	60% [4]
	Gene-targeted deletion/duplication analysis [5]	~10% [6]
Unknown [7, 8, 9]	NA	

NA = not applicable

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

4. In the largest study to date, 114 (62%) of 185 families studied had an identifiable *PRKAR1A* pathogenic variant [Bertherat et al 2009]. The variant detection frequency increases to 80% in individuals with Carney complex (CNC) presenting with Cushing syndrome caused by primary pigmented nodular adrenocortical disease (PPNAD) [Cazabat et al 2007].

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. In a study of 36 unrelated individuals with CNC who were negative for *PRKAR1A* single-nucleotide variants, two large *PRKAR1A* deletions were identified [Horvath et al 2008]. Of 51 individuals with CNC who were negative for other *PRKAR1A* pathogenic variants, 21.6% had a *PRKAR1A* deletion [Salpea et al 2014]. The deletions ranged from 328 bp to 3 Mb, affecting part or all of *PRKAR1A*; all deletions led to PRKAR1A haploinsufficiency.

7. Approximately 20% of families with CNC have been linked to 2p16 [Stratakis et al 1996].

8. Germline *PRKACA* duplications have been identified in five individuals (from four kindreds) with CNC who have adrenal tumors and Cushing syndrome [Beuschlein et al 2014]. In one of these kindreds, the duplication was inherited; in another individual, the duplication was *de novo* [Beuschlein et al 2014].

9. One individual with CNC had a germline rearrangement resulting in four copies of *PRKACB* [Forlino et al 2014]. *PRKACB* encodes the catalytic subunit Cβ of the cyclic AMP-dependent protein kinase A (PKA). Levels of Cβ and PKA activity were increased in the individual's lymphoblasts and fibroblasts; the authors propose that this is a CNC-causing gain-of-function variant.

Clinical Characteristics

Clinical Description

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. To date, more than 750 individuals have been identified with a pathogenic variant in *PRKAR1A*. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Carney Complex: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Skin pigment abnormalities	>70%	
Myxomas (cutaneous & mucosal)	>50%	
Cardiac myxoma	30%-50%	
Breast myxoma	30%-50%	
PPNAD	~25%	

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Somatomammotroph hyperplasia / GH-producing adenoma	≤75%	
LCCSCT	>50% of males	
Thyroid tumor(s)	≤75%	Mostly nonfunctioning thyroid follicular adenomas
PMS	~10%	

LCCSCT = large cell calcifying Sertoli cell tumor; GH = growth hormone; PMS = psammomatous melanotic schwannoma; PPNAD = primary pigmented nodular adrenocortical disease

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 eighth decade.
- 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 macules, 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 phenomenon (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 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. In a minority of individuals, PPNAD presents in the first two to three years; in the majority, it presents in the second or third decade. The hypercortisolism of PPNAD is usually insidious in onset. In children, hypercortisolism is manifest first as weight gain and growth arrest. In adults, long-standing hypercortisolism results in Cushing syndrome with central obesity, "moon facies," hirsutism, striae, hypertension, buffalo hump fat distribution, weakness, easy bruising, and psychological disturbance. Cushing syndrome is seen in 70% of affected females before age 45 years but in only 45% of affected males, similar to the higher frequency of Cushing syndrome in females in general. Histologic evidence of PPNAD has been found in almost every individual with CNC undergoing autopsy.

- **Growth hormone (GH)-producing pituitary adenomas.** 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 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.
- **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.
- **Testicular tumors.** Large cell calcifying Sertoli cell tumors (LCCSCTs) 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 LCCSCTs. The tumors are often multicentric and bilateral. LCCSCTs are almost always benign; malignancy has been reported only once, in an individual age 62 years. LCCSCTs 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 LCCSCTs include Leydig cell tumors and (pigmented nodular) adrenocortical rest tumors.
- **Ovarian cancer** can rarely be present in CNC, often developing in the background of chronic and large multiplex ovarian cysts.

Psammomatous melanotic schwannoma (PMS). This rare tumor of the nerve sheath occurs in approximately 10% of individuals with CNC. Malignant degeneration occurs in approximately 10% of PMS in 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).

Pancreatic tumors with various histology (e.g., adenocarcinoma, acinar cell carcinoma, intraductal papillary mucinous neoplasm) were found in 2.5% (9/354) of individuals from an international CNC registry.

Breast ductal adenoma is a benign tumor of the mammary gland ducts. It may be seen in individuals with CNC, although exact data about its frequency are lacking.

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. LCCSCTs cause replacement and obstruction of seminiferous tubules, macroorchidism, oligoasthenospermia, and inappropriate hormone production or aromatization. Despite these findings, fertility is frequently preserved.

Milder phenotypes. Most individuals with CNC meet diagnostic criteria. Very rarely, individuals may present with one clinical feature without any additional manifestations. These individuals can present with PPNAD or acromegaly only.

Genotype-Phenotype Correlations

Clinical and genotypic data on more than 380 affected individuals are available from more than 20 years of study at the National Institutes of Health (Bethesda, MD) and the Hospital Côchin (Paris). Phenotype analysis in 353 individuals with 80 different *PRKAR1A* pathogenic variants is summarized here [Bertherat et al 2009]:

- A *PRKAR1A* pathogenic variant was seen more often in individuals with the combination of myxomas (affecting multiple locations, e.g., skin, heart, and breast), PMS, thyroid tumors, and LCCSCTs than in individuals with CNC without this combination of findings.
- The "hot spot" pathogenic variant c.491_492delTG was more likely to be associated with lentigines, cardiac myxoma, and thyroid tumors than all other *PRKAR1A* pathogenic variants combined.
- Individuals with CNC heterozygous for a *PRKAR1A* pathogenic variant presented more frequently and earlier in life with pigmented skin lesions, myxomas, thyroid tumors, and gonadal tumors than those without an identifiable pathogenic variant. Tumors that presented at a significantly younger age in *PRKAR1A* heterozygotes than in individuals with CNC without an identifiable pathogenic variant included cardiac myxomas, thyroid tumors, and LCCSCTs.
- Those with isolated PPNAD (which was accompanied by lentiginosis in some individuals) diagnosed before age eight years were rarely heterozygous for a *PRKAR1A* pathogenic variant. The two *PRKAR1A* pathogenic variants commonly seen in those with isolated PPNAD were c.709-7_709-2delTTTTTA and c.1A>G (p.Met1Val) substitution affecting the initiation codon of the protein.
- *PRKAR1A* exon variants were associated more frequently with lentigines, PMS, acromegaly, and cardiac myxomas than intron variants, consistent with the observation that milder phenotypes are more likely to be associated with splice site variants than other types of pathogenic variants.
- Large *PRKAR1A* deletions (328 bp to 3 Mb) were associated with a variable phenotype that was generally more severe with unusual features, presumably as a result of haploinsufficiency of additional genes [Salpea et al 2014]. These individuals often have multiple additional clinical manifestations.

Penetrance

The overall penetrance of CNC in those with a *PRKAR1A* pathogenic variant is greater than 95% by age 50 years.

To date only two *PRKAR1A* pathogenic variants are known to result in incomplete penetrance of CNC: the splice site variant c.709-7_709-2delTTTTTA and the initiation-alternating substitution c.1A>G (p.Met1Val). When expressed, these two pathogenic variants lead to relatively mild CNC, manifesting mostly as PPNAD, which can be accompanied by lentigines [Groussin et al 2006].

Nomenclature

Carney complex has also been designated by the following acronyms:

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

"Carney triad" (OMIM 604287) is a completely different entity consisting of a triad of gastrointestinal stromal tumors, pulmonary chondroma, and extra-adrenal paraganglioma.

Prevalence

More than 750 individuals with CNC are known to the author.

Genetically Related (Allelic) Disorders

Acrodysostosis 1 with or without hormone resistance (OMIM 101800). These individuals do not have manifestations of CNC.

Sporadic tumors (including odontogenic myxomas, adrenal tumors, papillary thyroid cancer, and undifferentiated thyroid cancer, occurring as single tumors in the absence of any other findings of this syndrome) have been associated with a somatic variant in *PRKAR1A* that is **not** present in the germline

[Sandrini et al 2002, Bertherat et al 2003, Perdigão et al 2005]; thus, predisposition to these tumors is not heritable.

Differential Diagnosis

Genes of interest in the differential diagnosis of Carney complex (CNC) are summarized in Table 3.

Table 3. Genes of Interest in the Differential Diagnosis of Carney Complex

Gene / Genetic Mechanism	Disorder	MOI	Selected Features of Disorder Overlapping w/Carney Complex	Distinguishing Features / Comment
Abnormal regulation of gene transcription in BWS critical region [1]	Beckwith-Wiedemann syndrome (BWS)	See footnote 1.	Adrenal cortical tumors	No other common clinical features in BWS & CNC
AIP	*AIP* familial isolated pituitary adenomas (*AIP*-FIPA)	AD	GH-secreting pituitary adenomas (somatotropinomas) causing acromegaly	No other common clinical features in *AIP*-FIPA & CNC
BRAF *MAP2K1* *PTPN11* *RAF1*	Noonan syndrome w/ multiple lentigines (NSML)	AD	Lentigines	No other common clinical features in NSML & CNC
BRAF *KRAS* *LZTR1* *MAP2K1* *MRAS* *NRAS* *PTPN11* *RAF1* *RASA2* *RIT1* *RRAS2* *SOS1* *SOS2*	Noonan syndrome	AD AR [2]	Lentigines	No other common clinical features in Noonan syndrome & CNC
GNAS	Fibrous dysplasia / McCune-Albright syndrome (FD/MAS)	Not inherited	• Café au lait macules • Adrenal cortical tumors	Skeletal manifestations of FD/MAS do not occur in CNC.
LZTR1 *SMARCB1*	*LZTR1*- & *SMARCB1*-related schwannomatosis	AD	Schwannomas [3]	Meningiomas in some persons w/*SMARCB1*-related schwannomatosis
MEN1	Multiple endocrine neoplasia type 1	AD	• Adrenal cortical tumors • GH-secreting pituitary adenomas (somatotropinomas) causing acromegaly	Pancreatic & other neuroendocrine tumors are common in MEN1 but absent in CNC.
NF1	Neurofibromatosis 1	AD	• Café au lait macules • Schwannomas [3]	Gliomas & neurofibromas do not occur in CNC.
NF2	*NF2*-related schwannomatosis	AD	• Café au lait macules • Schwannomas [3]	• None of the other *NF2*-related tumors are present in CNC.

Table 3. continued from previous page.

Gene / Genetic Mechanism	Disorder	MOI	Selected Features of Disorder Overlapping w/Carney Complex	Distinguishing Features / Comment
PDE11A	Primary pigmented nodular adrenocortical disease 2 (PPNAD2) (OMIM 610475)	AD	Isolated micronodular adrenocortical hyperplasia	• In PPNAD2, there is usually little pigmentation in adrenal histology. • Persons w/PPNAD2 usually do not have other tumors.
PTEN	*PTEN* hamartoma tumor syndrome (PHTS)	AD	• Lentigines in Bannayan-Riley-Ruvalcaba syndrome [4] • Thyroid tumors in Cowden syndrome [4]	No other common clinical features in PHTS & CNC
STK11	Peutz-Jeghers syndrome	AD	• Lentigines • Large cell calcifying Sertoli cell tumors (tumors may be hormone producing)	Ovarian tumors similar to those seen in Peutz-Jeghers syndrome are not observed in CNC. [5]
TP53	Li-Fraumeni syndrome	AD	Adrenal cortical tumors	

AD = autosomal dominant; AR = autosomal recessive; CNC = Carney complex; GH = growth hormone; MOI = mode of inheritance
1. Beckwith-Wiedemann syndrome (BWS) is associated with abnormal regulation of gene transcription in two imprinted domains on chromosome 11p15.5 (also known as the BWS critical region). Regulation may be disrupted by any one of numerous mechanisms; reliable recurrence risk assessment requires identification of the genetic mechanism in the proband that underlies the abnormal expression of imprinted genes in the BWS critical region (see Beckwith-Wiedemann Syndrome).
2. Noonan syndrome is most often inherited in an autosomal dominant manner; Noonan syndrome caused by pathogenic variants in *LZTR1* can be inherited in either an autosomal dominant or an autosomal recessive manner.
3. CNC is the only genetic condition other than neurofibromatosis 1, neurofibromatosis 2, and isolated familial schwannomatosis in which schwannomas occur.
4. Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome are phenotypes observed in *PTEN* hamartoma tumor syndrome.
5. Stratakis et al [2000]

Other considerations

- **Skin.** Multiple lentigines also occur in benign familial lentiginosis (OMIM 151001), an autosomal dominant disorder of unknown genetic cause.
- **Epithelioid blue nevi** may occur in individuals who have no additional findings of CNC.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Carney complex (CNC), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Carney Complex: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Cardiac myxomas	Echocardiogram	Beginning in childhood
Cutaneous myxomas	Clinical exam for cutaneous myxomas	

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
PPNAD	Urinary free cortisol levels	Beginning in adolescence
	• Diurnal cortisol levels (11:30 pm, 12:00 am, & 7:30 am; 8:00 am sampling) • Dexamethasone stimulation test (modified Liddle's test) [1] • Adrenal CT exam	As needed
Pituitary adenomas	Serum IGF-1 levels	Beginning in adolescence
	• Pituitary MRI • Three-hour oral glucose tolerance test • 90-minute thyrotropin-releasing hormone testing	As needed for gigantism/acromegaly
Thyroid tumors	Thyroid ultrasonography	Beginning in adolescence
Testicular tumors	In males: • Testicular ultrasonography • Assessment of growth rate & pubertal staging	Beginning in childhood
Ovarian tumors	In females, transabdominal US of ovaries	Beginning in adolescence
Psammomatous melanotic schwannoma	Clinical assessment	These tumors may occur anywhere, & present w/mass effect signs/ symptoms.
	MRI (brain, spine, chest, abdomen, retroperitoneum, pelvis)	As needed
Pancreatic tumors	Abdominal imaging may be required if suggestive clinical signs.	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of Carney complex to facilitate medical & personal decision making

IGF-1 = insulin-like growth factor 1; MOI = mode of inheritance; PPNAD = primary pigmented nodular adrenocortical disease; US = ultrasound

1. Stratakis et al [1999]

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Carney Complex: Treatment of Manifestations

Manifestation/Concern	Treatment
Cardiac myxoma	Surgical excision via open heart surgery prior to development of heart dysfunction, stroke, or other embolism
Cutaneous & mammary myxoma	Surgical excision
Cushing syndrome	Bilateral adrenalectomy
Pituitary adenoma	Transsphenoidal surgery
Thyroid adenoma	Surgical resection for cancerous thyroid adenomas

Table 5. continued from previous page.

Manifestation/Concern	Treatment
LCCSCT	• Orchiectomy usually required for boys w/aggressively growing LCCSCTs & gynecomastia to avoid premature epiphyseal fusion & induction of central precocious puberty. • Boys w/mild gynecomastia & tumor that is not growing can be treated medically w/ aromatase inhibitors.
Ovarian tumor	Standard treatments per gynecologist/oncologist
Psammomatous melanotic schwannoma	Surgery to remove primary &/or metastatic lesions
Pancreatic tumor	Standard treatments per surgery/oncology

LCCSCT = large cell calcifying Sertoli cell tumor

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended for individuals with CNC and at-risk relatives.

Table 6. Carney Complex: Recommended Surveillance

System/Concern	Evaluation	Frequency
Cardiac myxomas	Echocardiogram	• Annually beginning in childhood (prior to puberty) • Biannually for those w/history of excised cardiac myxoma
Cutaneous myxomas	Clinical exam for cutaneous myxomas	As needed
PPNAD	Urinary free cortisol levels	Annually beginning in adolescence
	• Diurnal cortisol levels (11:30 pm, 12:00 am, & 7:30 am; 8:00 am sampling) • Dexamethasone stimulation test (modified Liddle's test) [1] • Adrenal CT exam	As needed
Pituitary adenomas	Serum IGF-1	Annually beginning in adolescence
	• Pituitary MRI • Three-hour oral glucose tolerance test • 90-minute thyrotropin-releasing hormone testing	As needed for those w/gigantism/ acromegaly
Thyroid tumors	Thyroid US	Annually beginning in adolescence
Testicular tumors	Monitoring of growth rate & pubertal staging	At each visit beginning in childhood in males
	Testicular US	Annually beginning in childhood in males
Ovarian tumors	Transabdominal US of ovaries	As needed to follow up abnormal findings in females
Psammomatous melanotic schwannoma	• Clinical assessment for mass effects • MRI (brain, spine, chest, abdomen, retroperitoneum, pelvis) in those w/suspected tumor	As needed

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Pancreatic tumors	Clinical exam for mass effects	As needed

IGF-1 = insulin-like growth factor 1; PPNAD = primary pigmented nodular adrenocortical disease; US = ultrasound
1. Stratakis et al [1999]

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing of the *PRKAR1A* pathogenic variant in the family in order to identify as early as possible those who would benefit from initiation of surveillance and treatment.

When molecular genetic testing for a *PRKAR1A* pathogenic variant is not possible or is not informative, individuals at 50% risk (i.e., first-degree relatives of an individual with CNC) should undergo surveillance (see Table 6).

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

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 PRKAR1A* pathogenic variant [Stelmachowska-Banas et al 2017].
- If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

- The family history of some individuals diagnosed with CNC 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. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

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 and/or known to be heterozygous for a *PRKAR1A* pathogenic variant, the risk to the sibs is 50%.
- If the proband has a known *PRKAR1A* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband

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

Other family members. The risk to the other family members depends on the status of the proband's parents: if a parent is affected and/or known to be heterozygous for a *PRKAR1A* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

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

Predictive testing of at-risk asymptomatic adults and children

- If a clinically diagnosed relative has undergone molecular genetic testing and is found to have a pathogenic variant in *PRKAR1A*, molecular genetic testing can be used with certainty to clarify the genetic status of at-risk family members.
- It is appropriate to consider molecular genetic testing of young at-risk family members in order to guide medical management (see Management, Evaluation of Relatives at Risk).

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is 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. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *PRKAR1A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Carney Complex Community**
  www.carneycomplex.org
- **MedlinePlus**
  Carney complex
- **American Cancer Society**
  Phone: 800-227-2345
  cancer.org
- **American Heart Association**
  Phone: 800-242-8721
  heart.org
- **CancerNetwork.com**
  www.cancernetwork.com
- **National Cancer Institute (NCI)**
  Phone: 800-422-6237
  Email: NCIinfo@nih.gov
  cancer.gov

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Carney Complex: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

PRKAR1A	17q24.2	cAMP-dependent protein kinase type I-alpha regulatory subunit	PRKAR1A database PRKAR1A Mutation Database	PRKAR1A	PRKAR1A

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Carney Complex (View All in OMIM)

160980	CARNEY COMPLEX, TYPE 1; CNC1
188830	PROTEIN KINASE, cAMP-DEPENDENT, REGULATORY, TYPE I, ALPHA; PRKAR1A
605244	CARNEY COMPLEX, TYPE 2; CNC2

Molecular Pathogenesis

Haploinsufficiency of cAMP-dependent protein kinase type I-alpha regulatory subunit (PRKAR1A) causes Carney complex (CNC). In tumors of individuals affected with CNC, biallelic inactivation of *PRKAR1A* leads to enhanced intracellular signaling by protein kinase A (PKA), as evidenced by an almost twofold greater response to cAMP in CNC tumors than in non-CNC tumors [Groussin et al 2002].

The mechanism is therefore loss of function of a protein that controls almost all of cAMP signaling in all cells. PRKAR1A regulates the catalytic subunit of PKA, which when uncontrolled due to PRKAR1A's loss of function causes increased endocrine hormone signaling and the formation of tumors [Zawadzki & Taylor 2004]. Thus, *PRKAR1A* is a tumor suppressor gene.

Mechanism of disease causation. Loss of function

Table 7. *PRKAR1A* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_002734.5 NP_002725.1	c.1A>G	p.Met1Val	See Genotype-Phenotype Correlations [Kirschner et al 2000].
	c.491_492delTG	p.Val164ArgfsTer5	• Common variant • See Genotype-Phenotype Correlations [Kirschner et al 2000].
NM_002734.5	c.709-7_709-2delTTTTTA	--	See Genotype-Phenotype Correlations [Groussin et al 2006].

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Dr Stratakis has moved from the US National Institutes of Health to the Foundation for Research & Technology Hellas (FORTH) in Greece.

Dr Stratakis is actively involved in clinical research regarding individuals with CNC. Dr Stratakis would be happy to communicate with persons who have any questions regarding diagnosis of Carney complex (CNC) or other considerations.

Dr Stratakis is also interested in hearing from clinicians treating families affected by CNC in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Dr Stratakis to inquire about review of *PRKAR1A* variants of uncertain significance.

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- 22 March 2005 (me) Comprehensive update posted live
- 5 February 2003 (me) Review posted live
- 7 October 2002 (cs) Original submission

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