Carney complex (CNC)

Identity

Note A multiple neoplasia syndrome characterized by spotty skin pigmentation, cardiac and other myxomas, endocrine tumors, psammomatous melanotic schwannomas and other tumors.

Inheritance A genetically heterogeneous autosomal dominant disorder with high penetrance for CNC1 (penetrance for CNC1 due to PRKARIA defects is close to 100%); this estimate of penetrance does not apply to kindreds with CNC2 because the CNC2 gene (s) is still unknown. Most of the cases of CNC (70%) are familial.

Clinics

Phenotype and clinics Developmental disorder. In some cases the disease is diagnosed at birth. Onset of the disease occurs commonly at a young age and the median age at detection is 20 years.

Spotty skin pigmentation lesions, such as lentigines (small, brown to black, non or slightly elevated, round or irregular) and blue nevi (large, blue to black, domed lesion) observed primarily in the face, eyelids, ears, and borders of the lips are the most common clinical manifestation of CNC (77%). Lentigines tend to fade with the age, usually after the fourth decade of life.

Myxomas are frequent lesions in CNC patients; heart myxomas (53%) occur multicentrically, and in any, or all, cardiac chambers; skin myxomas (33%) are detected in the eyelid, the external ear canal, the nipple, the oropharynx, the female genital tract and the female pelvis. Breast myxomas are often bilateral and present in more than 70% of adult women with CNC.

Psammomatous melanotic shwannomas , very rare tumors (10%), may occur anywhere in the peripheral nervous system, but most frequently in the gastrointestinal tract and paraspinal symphatetic chain.

Breast ductal adenomas, unusual mammary tumors akin to intraductal papillomas have been detected in 3% of CNC cases.

Endocrine lesions in CNC include testicular neoplasms (33%), primary pigmented nodule adrenocortical disease (PPNAD) (26%), growth hormone (GH) and prolactin-producing pituitary tumors (14%) and thyroid cancer (5%).

Neoplastic risk

Skin lesions are benign.

Heart, skin and breast myxomas are benign lesions.

Psammomatous melanotic shwannoma may be malignant and metastasizes aggressively to lungs, brain and other organs

Breast ductal adenomas are benign but malignancy was detected in one case

Testicular tumors are almost always benign; metastasis has been reported only in one older patient.

PPNAD in CNC is always benign.

Growth hormone and prolactin-producing pituitary tumors are benign lesions.

Thyroid neoplasms may also become malignant.

Treatment: Annual studies: echocardiogram (note that in pediatric patients it should be done during the first 6 months of life and annually thereafter), measurement of urinary free cortisol and serum IGF-1 levels, thyroid ultrasonography, testicular ultrasonography for male and transabdominal pelvic ultrasonography for females; surgery when necessary. Additional clinical and imaging studies may be necessary for the detection of PPNAD and GH-producing pituitary adenoma.

Prognosis: According to the severity of the disease in a given patient, and to the quality of a regular follow up, life span is decreased in patients with CNC. 57% of the deaths are due to heart related causes; others due to the postoperative complications or evolution of the maligant process; a presymptomatic diagnosis improves survival data and might prevent earlier the main causes of death in this disease.

Genes involved and Proteins

Gene Name PRKARIA

Location: 17q23-24

Note: Mutations in PRKARIA are found in about 46 % of cases of CNC syndrome; there is genetic heterogeneity, and unknown gene(s) on 2p16 is probably also responsible for the disease.

DNA/RNA

Description: 10 exons

Protein

Description: 48 kDa; contains two tandem cAMP-binding domains at the C-terminus and the dimerization domain at the N-terminus that serves also as a docking site for A Kinase Anchoring Proteins (AKAPs).

Expression: Ubiquitously expressed, in particular in brain, endocrine tissues, adipose tissue and bone.

Function: The function of PRKAR1A is to bind cAMP and regulate the function of the catalytic subunits of the protein kinase A (PKA) holoenzyme. Two regulatory subunits bind two catalytic subunits forming an inactive PKA tetramer. Activation of PKA occurs when 2 cAMP molecules bind to each regulatory subunit eliciting a reversible conformational change that releases active catalytic subunits. Four different regulatory subunits and three catalytic subunits of PKA have been identified in humans. The protein encoded by this gene is one of the regulatory subunits. It may act as a tumor-suppressor in CNC and other tumors.

Mutations

Germinal: Most mutations are null alleles; they are dispersed through the coding region of the gene, involving every exon except 4A, 9 and 10.

Somatic: Many of CNC tumors show loss of heterozygosity.

Gene Name CNC2

Location 2p16

DNA/RNA

Description Unknown

Protein

Function Unknown

Mutations

Somatic Many of CNC tumors show amplification or deletion of the 2p16 region.

Bibliography

Lentiginosis and left atrial myxoma.
Rees JR, Ross FGM, Keen G.
Brit Heart J 1973; 35: 874-876.
Medline 4729862

A syndrome of various cutaneous pigmented lesions, myxoid neurofibromata and atrial myxoma: the N.A.M.E. syndrome.
Atherton DJ, Pitcher DW, Wells RS, MacDonald DM.
Brit J Derm 1980; 103: 421-429.
Medline 7437308

Large-cell calcifying Sertoli cell tumor of the testis.
Proppe KH, Scully RE.
Am J Clin Path 1980; 74: 607-619.
Medline 7446466

Familial Cushing's syndrome with primary adrenocortical microadenomatosis (primary adrenocortical nodular dysplasia).
Schweizer-Cagianut M, Froesch ER, Hedinger C.
Acta Endocr 1980; 94: 529-535.
Medline 6254301

Primary adrenocortical nodular dysplasia with Cushing's syndrome and cardiac myxomas: a peculiar familial disease.
Schweizer-Cagianut M, Salomon F, Hedinger CE.
Virchows Arch Path Anat 1982; 397: 183-192.
Medline 7179736

The triad of gastric epithelioid leiomyosarcoma, pulmonary chondroma, and functioning extra-adrenal paraganglioma: a five-year review.
Carney JA.
Medicine 1983; 62: 159-169.
Medline 6843355

Mucocutaneous lentigines, cardiomucocutaneous myxomas, and multiple blue nevi: the 'LAMB' syndrome.
Rhodes AR, Silverman, RA, Harrist TJ, Perez-Atayde AR.
J Am Acad Derm 1984; 10: 72-82.
Medline 6693605

Bilateral primary pigmented nodular adrenocortical disease: rare cause of the

Cushing syndrome.
Shenoy BV, Carpenter PC, Carney JA.
Am J Surg Path 1984; 8: 335-344.
Medline 6329005

The complex of myxomas, spotty pigmentation, and endocrine overactivity.
Carney JA, Gordon H, Carpenter PC, Shenoy BV, Go VL.
Medicine (Baltimore) 1985; 64: 270-283.
Medline 4010501

Carney's complex.
Bain J.
Mayo Clin Proc 1986; 61: 508.
Medline 3713260

Cutaneous myxomas: a major component of the complex of myxomas, spotty pigmentation, and endocrine overactivity.
Carney JA, Headington JT, Su WPD.
Arch Derm 1986; 122: 790-798.
Medline 3729510

Dominant inheritance of the complex of myxomas, spotty pigmentation, and endocrine overactivity.
Carney JA, Hruska LS, Beauchamp GD, Gordon H.
Mayo Clin Proc 1986; 61: 165-172.
Medline 3945116

A familial syndrome of cardiac myxomas, myxoid neurofibromata, cutaneous pigmented lesions, and endocrine abnormalities.
Wilsher ML, Synek BJL, Roche AHG, Holdaway IM, Neutze JM, Nicholson GI.
Aust New Zeal J Med 1986; 16: 393-396.
Medline 3465316

Ocular pigmented spots and eyelid myxomas.
Kennedy RH, Waller RR, Carney JA.
Am J Ophthal 1987; 104: 533-538
Medline 3674187

'Syndrome myxoma': a subset of patients with cardiac myxoma associated with pigmented skin lesions and peripheral and endocrine neoplasms.
Vidaillet HJ Jr, Seward JB, Fyke FE III, Su WPD, Tajik AJ.
Brit Heart J 1987; 57: 247-255.
Medline 3566983

Hypersecretion of growth hormone and prolactin in McCune-Albfight syndrome.
Cuttler L, Jackson JA, Saeed uz-Zafar, Levitsky LL, Mellinger RC, Frohman LA.
J Clin Endocrinol Metab 1989; 68:1148-1154.
Medline Medline

Familial Cushing's syndrome due to primary pigmented nodular adrenocortical disease: reinvestigation 50 years later.
Young WF Jr, Carney JA, Musa BU, Wulffraat NM, Lens JW, Drexhage HA.
New Eng J Med 1989; 321: 1659-1664.
Medline 2586567

Autosomal dominant transmission of the N.A.M.E. syndrome (nevi, atrial myxoma, mucinosis of the skin and endocrine overactivity).
Koopman RJJ, Happle R.
Hum Genet 1991; 86: 300-304.
Medline 1997386

Multiple lentigines, myxoid tumours and endocrine overactivity; four cases of Carney's complex.
Handley J, Carson D, Sloan J, Walsh M, Thornton C, Hadden D, Bingham EA.
Brit J Derm 1992; 126: 367-371.
Medline 1571257

Acromegaly and hyperprolactinemia in a patient with polyostotic fibrous dysplasia: dynamic endocrine studies and treatment with the somatostatin analogue octreotide.
Garcia MB, Koppeschaar HP, Lips CJ, Thijsen JH, Krenning EP.
J Endocrinol Invest 1994; 17: 59-65.
Medline 7911814

Carney complex: the complex of myxomas, spotty pigmentation, endocrine veractivity, and schwannomas.
Carney JA.
Semin Dermatol 1995; 14: 90-98.
Medline 7640202

The search for Harvey Cushing's patient, Minnie G., and the cause of her hypercortisolism.
Carney JA.
Am J Surg Path 1995; 19: 100-108.
Medline 780212

Ductal adenoma of the breast and the Carney complex.
Carney JA, Stratakis CA.
Am J Surg Pathol 1996; 20: 1154-1155.
Medline 8764753

Sporadic cardiac myxomas and tumors from patients with Carney complex are not associated with activating mutations of the Gs_ gene.
DeMarco L, Stratakis CA, Boson WL, Yakbovitz O, Carson E, Adrade LM, Amaral VF, Rocha JL, Choursos GP, Nordenskjold M & Friedman E.
Hum Genet 1996; 98: 185-188.
Medline 8698339

Carney complex, a familial multiple neoplasia and lentiginosis syndrome.

Analysis of 11 kindreds and linkage to the short arm of chromosome 2.
Stratakis CA, Carney JA, Lin JP, Papanicolaou DA, Karl M, Kastner DL, Pras E, Chrousos GP.
J Clin Invest 1996; 97: 699-705.
Medline 8609225

Cytogenetic and microsatellite alterations in tumors from patients with the syndrome of myxomas, spotty skin pigmentation, and endocrine overactivity (Carney complex).
Stratakis CA, Jenkins RB, Pras E, Mitsiadis CS, Raff SB, Stalboerger PG, Tsigos C, Carney JA, Chrousos GP.
J Clin Endocrinol Metab 1996; 81: 3607-3614.
Medline 8855810

Genetic heterogeneity of familial atrial myxoma syndromes (Carney complex).
Basson CT, MacRae CA, Korf B, Merliss A.
Am J Cardiol 1997; 79: 994-995.
Medline 9104925

Spectrum of malignancy and premalignancy in Carney syndrome.
Nwokoro NA, Korytkowski MT, Rose S, Gorin MB, Stadler MP, Witchel SF, Mulvihill JJ.
Am J Med Genet 1997; 73: 369-377.
Medline 9415461

Testicular ultrasound in Carney complex: report of three cases.
Premkumar A, Stratakis CA, Shawker TH, Papanicolaou DA, Chrousos GP.
J Clin Ultrasound 1997; 25: 211-214.
Medline 9142622

Primary pigmented nodular adrenocortical disease: reevaluation of a patient with carney complex 27 years after unilateral adrenalectomy.
Sarlis NJ, Chrousos GP, Doppman JL, Carney JA, Stratakis CA.
J Clin Endocrinol Metab 1997; 82: 1274-1278.
Medline 9100606

Thyroid gland abnormalities in patients with the syndrome of spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas (Carney complex).
Stratakis CA, Courcoutsakis NA, Abati A, Filie A, Doppman JL, Carney JA, Shawker T.
J Clin Endocrinol Metab 1997; 82: 2037-2043.
Medline 9215269

Epithelioid blue nevus and psammomatous melanotic schwannoma: the unusual pigmented skin tumors of the Carney complex.
Carney JA, Stratakis CA.
Semin Diagn Pathol 1998; 15: 216-224.
Medline 9711672

Identification of a novel genetic locus for familial cardiac myxomas and Carney complex.
Casey M, Mah C, Merliss AD, Kirschner LS, Taymans SE, Denio AE, Korf B, Irvine AD, Hughes A, Carney JA, Stratakis CA, Basson CT.
Circulation 1998; 98: 2560-2566.
Medline 9843463

Evidence for a second genetic locus in Carney complex.
Irvine AD, Armstrong DK, Bingham EA, Hadden DR, Nevin NC, Hughes AE.
Br J Dermatol 1998; 139:572-576.
Medline 9892898

Characterization of the adrenal gland pathology of Carney complex, and molecular genetics of the disease.
Kirschner LS, Taymans SE, Stratakis CA.
Endocr Res 1998; 24: 863-864.
Medline 9888588

Syndrome of myxomas, spotty skin pigmentation, and endocrine overactivity (Carney complex).
Legius E,Daenen W, Vandenbergh V, Verbeeck G, Bex M, Fryns JP.
Genet Counsel 1998; 9: 287-290.
Medline 9894167

Clinical and genetic analysis of primary bilateral adrenal diseases (micro- and macronodular disease) leading to Cushing syndrome.
Stratakis CA, Kirschner LS
Horm Metab Res 1998; 30: 456-463.
Medline 9694579

Carney complex: diagnosis and management of the complex of spotty skin pigmentation, myxomas, endocrine overactivity & schwannomas
Stratakis CA, Kirschner LS, Carney JA.
Am J Med Genet 1998; 80: 183-185.
Medline 9805140

Carney complex, Peutz-Jeghers syndrome, Cowden disease, and Bannayan-Zonana syndrome share cutaneous and endocrine manifestations, but not genetic loci.
Stratakis CA, Kirschner LS, Taymans SE, Tomlinson IP, Marsh DJ, Torpy DJ, Giatzakis C, Eccles D M, Theaker J, Houlston RS, Blouin JL, Antonarakis SE, Basson CT, Eng C, Carney JA.
J Clin Endocrinol Metab 1998; 83: 2972-2976.
Medline 9709978

Molecular genetic diagnosis of the familial myxoma syndrome (Carney complex).
Goldstein MM, Casey M, Carney JA, Basson CT.
Am J Med Genet 1999; 86: 62-65.
Medline 10440831

Genomic mapping of chromosomal region 2p15-p21 (D2S378-D2S391): integration of Genemap'98 within a framework of yeast and bacterial artificial chromosomes.
Kirschner LS, Taymans SE, Pack S, Pak E, Pike BL, Chandrasekharappa SC, Zhuang Z, Stratakis CA.
Genomics 1999; 62: 21-33.
Medline 10585764

Paradoxical response to dexamethasone in the diagnosis of primary pigmented nodular adrenocortical disease.
Stratakis CA, Sarlis N, Kirschner LS, Carney JA, Doppman JL, Nieman LK, Chrousos GP, Papanicolaou DA.
Ann Intern Med 1999; 131: 585-591.
Medline 10523219

Radiation hybrid mapping of chromosomal region 2p15-p16: integration of expressed and polymorphic sequences maps at the Carney complex (CNC) and Doyne honeycomb retinal dystrophy (DHRD) loci.
Taymans SE, Kirschner LS, Giatzakis C, Stratakis CA.
Genomics 1999; 56: 344-349.
Medline 10087203

Mutations of the gene encoding the protein kinase A type I-alpha regulatory subunit in patients with the Carney complex.
Kirschner LS, Carney JA, Pack SD, Taymans SE, Giatzakis C, Cho YS, Cho-Chung YS, Stratakis CA.
Nat Genet 2000; 26: 89-92
Medline 10973256

Genetic heterogeneity and spectrum of mutations of the PRKAR1A gene in patients with the carney complex.
Kirschner LS, Sandrini F, Monbo J, Lin JP, Carney JA, Stratakis CA.
Hum Mol Genet 2000; 9: 3037-3046.
Medline 11115848

Genetic and histologic studies of somatomammotropic pituitary tumors in patients with the "complex of spotty skin pigmentation, myxomas, endocrine overactivity and schwannomas" (Carney complex).
Pack SD, Kirschner LS, Pak E, Zhuang Z, Carney JA, Stratakis CA.
J Clin Endocrinol Metab 2000; 85(10): 3860-3865.
Medline 11061550

Prolactin secretion abnormalities in patients with the "syndrome of spotty skin pigmentation, myxomas, endocrine overactivity and schwannomas" (Carney complex).
Raff SB, Carney JA, Krugman D, Doppman JL, Stratakis CA.
J Pediatr Endocrinol Metab 2000 Apr; 13(4): 373-379.
Medline 10776991

Ovarian lesions in Carney complex: clinical genetics and possible predisposition to malignancy.
Stratakis CA, Papageorgiou T, Premkumar A, Pack S, Kirschner LS, Taymans SE, Zhuang Z, Oelkers WH, Carney JA.
J Clin Endocrinol Metab 2000; 85(11): 4359-4366.
Medline 11095480

The neurosurgical implications of Carney complex.
Watson JC, Stratakis CA, Bryant-Greenwood PK, Koch CA, Kirschner LS, Nguyen T, Carney JA, Oldfield EH.
J Neurosurg 2000; 92:413-418.
Medline 10701527

Osteochondromyxoma of bone: a congenital tumor associated with lentigines and other unusual disorders.
Carney JA, Boccon-Gibod L, Jarka DE, Tanaka Y, Swee RG, Unni KK, Stratakis CA.
Am J Surg Pathol 2001; 25: 164-176.
Medline 11176065

Multiple lentigines associated with cutaneous myxomas.
Egan CA, Stratakis CA, Turner ML.
J Am Acad Dermatol 2001; 44: 282-284.
Medline 11174387

Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation.
Stratakis CA, Kirschner LS, Carney JA.
J Clin Endocrinol Metab 2001; 86: 40414046.
Medline 11549623

Molecular analysis of the cyclic AMP - dependent protein kinase A (PKA) regulatory subunit 1A (PRKAR1A) gene in patients with Carney Complex and primary pigmented nodular adrenocortical disease (PPNAD) reveals novel mutations and clues for pathophysiology: augmented PKA signaling is associated with adrenal tumorigenesis in PPNAD.
Groussin L, Kirschner LS, Vincent-Dejean C, Perlemoine K, Jullian E, Delemer B, Zacharieva S, Pignatelli D, Carney JA, Luton JP, Bertagna X, Stratakis CA, Bertherat J.
Am J Hum Genet 2002; 71: 1433-1442.
Medline 12424709

Pituitary adenoma in Carney complex: an immunohistochemical, ultrastructural, and immunoelectron microscopic study.
Kurtkaya-Yapicier O, Scheithauer BW, Carney JA, Kovacs K, Horvath E, Stratakis CA, Vidal S, Vella A, Young WF Jr, Atkinson JL, Lloyd RV, Kontogeorgos G.
Ultrastruct Pathol 2002; 26: 345-353.
Medline 12537759

Ovarian tumors associated with multiple endocrine neoplasias and related syndromes (Carney complex, Peutz-Jeghers syndrome, von Hippel-Lindau

disease, Cowden¹s disease).
Papageorgiou T, Stratakis CA.
Int J Gynecol Cancer 2002; 12(4): 337-347.
Medline 12144681

PRKAR1A, one of the Carney complex genes, and its locus (17q22-24) are rarely altered in pituitary tumours outside the Carney complex.
Sandrini F, Kirschner LS, Bei T, Farmakidis C, Yasufuku-Takano J, Takano K, Prezant TR, Marx SJ, Farrell WE, Clayton RN, Groussin L, Bertherat J, Stratakis CA.
J Med Genet 2002; 39(12): e78.
Medline 12471216

Chromosome 2 (2p16) abnormalities in Carney complex tumours.
Matyakhina L, Pack S, Kirschner LS, Pak E, Mannan P, Jaikumar J, Taymans SE, Sandrini F, Carney JA, Stratakis CA.
J Med Genet 2003; 40(4): 268-277.
Medline PubMed

Clinical and molecular genetics of Carney complex.
Sandrini F, Stratakis C.
Mol Genet Metab 2003; 78(2): 83-92.
Medline 12666684

Human tumors associated with Carney complex and germline PRKAR1A mutations: a protein kinase A disease!
Stergiopoulos S, Stratakis CA.
FEBS Lett. 2003; 546:59-64.
Medline 12829237

A typical Korean case of Carney complex.
Yoon HD, Shon HS.
Korean J Intern Med 2003; 18(4): 260-265.
Medline PubMed

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