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Cancer Prone Disease Section

Mini Review

Carney complex (CNC)

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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

PRKARIA

Alias

HGNC:9388; CAR; CNC1; MGC17251; PKR1; PRKAR1; TSE1

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.

CNC2

Location

2p16

DNA/RNA

Description: Unknown.

Protein

Function: Unknown.

Mutations

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

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