ENDOCRINOLOGÍA Y NUTRICIÓN
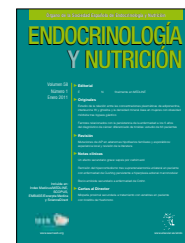
REVIEW

Carney complex

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Abstract   Carney complex (CNC) is an autosomal dominantly inherited syndrome characterized by spotty skin pigmentation, cardiac and cutaneous myxoma, and endocrine overactivity. Skin pigmentation includes lentigines and blue nevi. Myxomas may occur in breast, skin and heart. Cardiac myxomas may be multiple and occur in any cardiac chamber, and are more prone to recurrence. The most common endocrine gland manifestation is an ACTH-independent Cushing's syndrome due to primary pigmented nodular adrenocortical disease (PPNAD). PPNAD may occur in isolation, with no other signs of CNC. The pituitary and thyroid glands and gonads are also involved.

The PRKAR1A gene, located in 17 q22-24, encodes for the type 1A regulatory subunit of protein kinase A. Inactivating germline mutations of this gene are found in 70% of patients with CNC. PRKAR1A is a key component of the c-AMP signaling pathway that has been implicated in endocrine tumorigenesis. Many different mutations have been reported in the PRKAR1A gene. In almost all cases the sequence change was predicted to lead to a premature stop codon and the resultant mutant mRNA was subject to nonsense-mediated mRNA decay. There is no clear genotype-phenotype correlation in patients with CNC.

Genetic analysis should be performed in all CNC index cases. All affected patients should be monitored for clinical signs of CNC at least once a year. Genetic diagnosis allows for the more effective preparation of appropriate and effective therapeutic strategies and genetic counseling for patients and gene carriers, and prevents unnecessary tests being given to relatives not carrying the gene.
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Complejo de Carney

Resumen El complejo de Carney (CNC) es un síndrome de herencia autosómica dominante caracterizado por mixomas en diferentes localizaciones, hiperpigmentación cutánea y afectación de glándulas endocrinas. La afectación cutánea más característica es la presencia de lentiginosis y nevus azules. Los mixomas pueden hallarse en tejido subcutáneo, mamario o en región cardíaca. Los mixomas cardíacos pueden ser múltiples, localizados en cualquier cámara cardíaca y presentan mayor riesgo de recurrencia. La manifestación endocrinológica más frecuente es la presencia de un síndrome de Cushing independiente de ACTH debido a enfermedad adrenocortical nodular pigmentada primaria (primary pigmented nodular adrenal disease o PPNAD). La PPNAD puede manifestarse de manera aislada sin otras manifestaciones del CNC. Otras glándulas afectadas son la hipófisis, tiroides y gónadas.

El gen PRKAR1A localizado en 17q22-24 codifica la subunidad reguladora R1A de la proteína kinasa A. Mutaciones inactivantes de este gen se encuentran en un 70% de pacientes con CNC. PRKAR1A es un componente clave de la vía celular de señalización del AMPc implicado en la presencia de tumorogénesis de origen endocrinológico. Se han descrito numerosas mutaciones en el gen PRKAR1A y la práctica totalidad de ellas conllevan cambios en la secuencia que dan lugar a codones de terminación prematuros y el RNAm resultante es degradado por la mRNA nonsense mediated decay. No existe una clara relación entre genotipo y fenotipo en los pacientes con CNC.

Se ha de realizar estudio genético en todos los casos índice. El seguimiento para todas las manifestaciones clínicas del CNC deberían realizarse anualmente en los pacientes afectados. El estudio genético posibilita preparar de manera más efectiva nuevas estrategias terapéuticas y consejo genético para los pacientes y portadores, y evita la realización de pruebas innecesarias en familiares no portadores.

Introduction

Carney complex (CNC) (MIM:160980) was first reported in 1985 by J. Aidan Carney et al. as a combination of myxomas, spotty skin pigmentation, and endocrine overactivity. The description of this new syndrome led to the conclusion that a vast majority of patients previously characterized as suffering different conditions known by the acronyms NAME (nevi, atrial myxoma, ephelides) and LAMB (lentigines, atrial myxoma, blue nevi) should be considered to have CNC. CNC is an autosomal, dominantly inherited syndrome that shows variable expressivity and almost complete penetrance (70%-80% at 40 years). CNC could be considered as a form of multiple endocrine neoplasia because of the frequent involvement of two or more endocrine glands, causing primary pigmented nodular adrenal disease (PPNAD), pituitary adenomas secreting GH and PRL, testicular tumors, nodular thyroid disease, and ovarian cysts. Some of these conditions, such as PPNAD, are highly specific to CNC[1,2].

Current diagnosis of this syndrome is based on the presence of two or more of its typical manifestations, as confirmed by histology, laboratory tests, or imaging tests. However, if the patient is a known carrier of an inactivating mutation of the type 1 alpha regulatory subunit of protein kinase A (PRKAR1A) or is a first-degree relative of a patient with CNC, a single clinical manifestation is required to diagnose the disease[3] (Table 1).

Determination of inactivating mutations of the type 1A (R1A) regulatory subunit of protein kinase A gene (PRKAR1A)

Table 1 Diagnostic criteria of Carney complex.

- Typically distributed lentigines (lips, conjunctiva, oral and genital mucosa)
- Myxoma (in skin or mucosa)[a]
- Cardiac myxoma
- Breast myxomatosis[a] or MRI image (in fat suppression mode) suggesting diagnosis
- PPNAD[a] or paradoxical positive corticosteroid response in urine after dexamethasone administration during Liddle test
- Acromegaly secondary to GH-secreting adenoma[a]
- LCCSCT[a] or presence of characteristic calcifications in testicular ultrasound
- Thyroid carcinoma[a] or presence of multiple hypoechoic nodules in thyroid ultrasound in a young patient
- Psammomatous melanocytic schwannoma[a]
- Blue nevus, multiple epithelioid blue nevi[a]
- Multiple ductal adenomas of the breast[a]
- Osteochondromyxoma

Additional criteria
- First-degree relative affected
- Inactivating mutation in the PRKAR1A gene

For CNC diagnosis, patients must show: 1) two or more of the above listed clinical manifestations, or 2) one clinical manifestation and one additional criterion (first-degree relative affected or inactivating mutation in the PRKAR1A gene). LCCSCT: large-cell calcifying Sertoli cell tumor); PPNAD: primary pigmented nodular adrenal disease.
[a]Requires histological confirmation.

in most patients with CNC has made it possible to estimate its penetrance, validating diagnostic criteria for the disease, and showing that no clear phenotype-genotype correlation exists.

Epidemiology

CNC is an extremely uncommon disease. Approximately 600 cases have been reported, and the largest series, consisting of 353 patients, was reported in 2009 by the Mayo Clinic and Cochin Hospital. Data from this series suggest a greater prevalence in females (63%) and diagnosis of the condition during the second and third decades of life. Seventy-three percent of patients had inactivating mutations in the PRKAR1A gene. Cases have been reported in all ethnic groups[4].

Non-endocrine clinical manifestations

Skin lesions

The most common clinical sign in CNC is lentiginosis. Lentiginosis is very useful for diagnosis because it is highly characteristic and usually occurs early in the course of CNC. Lentiginosis may already occur at birth, but its typical distribution is not seen until adolescence. It tends to disappear during the fourth decade of life. Distribution around the upper and lower lips, conjunctiva, and oral and genital mucosa is characteristic.

Cutaneous myxomas are smooth subcutaneous papules or nodules of a pearly or pink color. Lesions are usually multiple and preferentially located in the external auditory canal, eyelids, and breast area.

Multiple blue nevi and epithelioid blue nevi are frequently found.

Cardiac myxoma

Cardiac myxoma is the most common non-cutaneous manifestation. It accounts for more than 50% of mortality in patients with CNC, secondary to embolic events, heart failure, or valve occlusion. Cardiac myxoma may occur in any cardiac chamber, be multiple, and show a greater aggressiveness and recurrence rate as compared to sporadic forms.

Other tumors

There are other tumors which very rarely occur in CNC, but are highly specific to the condition. Psammomatous melanocytic schwannoma occurs in the peripheral and central nervous system, most commonly in the gastrointestinal tract. Its name derives from its characteristic hyperpigmentation due to melanin accumulation with frequent calcification. Other characteristic tumors include ductal adenoma of the breast, breast myxoma, and osteochondromyxoma[3,5-7].

Endocrine manifestations

Primary pigmented nodular adrenocortical disease

Clinical signs
PPNAD is a very uncommon cause of ACTH-independent Cushing's syndrome (< 1%). PPNAD usually occurs in the setting of CNC and is the most common endocrine gland tumor. PPNAD incidence in CNC patients at diagnosis is 26%. PPNAD may also be diagnosed in the absence of other signs of CNC or family history of the disease (isolated PPNAD). Mean age at diagnosis is 34 years, and the condition is significantly more common in females (71%), in whom it is also diagnosed at an earlier age (30 years, as compared to 46 years in males)[4].

The name of the disease is due to its gross appearance, characterized by small hyperpigmented nodules in the cortex of both adrenal glands, although bigger nodules have also been reported.

Diagnosis of Cushing's syndrome in PPNAD may be difficult because hypercortisolism may appear in very different forms. It may be slowly progressive, explosive, cyclic, asymptomatic (subclinical forms), or resolve spontaneously in some cases. Paucisymptomatic or asymptomatic forms are usually diagnosed by routine screening of patients with PPNAD, either patients with other clinical manifestations of the disease or relatives.

Despite these variable presentation forms, the clinical signs secondary to hypercortisolism are similar to those of all other conditions causing Cushing's syndrome (trunkal obesity, weight gain, red striae, muscle weakness, osteoporosis, and low height in children[3-7].

Hormone study
High urinary free cortisol levels are usually found at PPNAD diagnosis in most patients, although these levels may be highly variable. Cortisol circadian rhythm is abolished, and plasma ACTH levels are suppressed. A discrepancy between suppressed plasma ACTH levels and plasma or urine cortisol levels within normal ranges is often found in forms with only a few symptoms. No cortisol or ACTH accumulation occurs after CRH stimulation[5-8] No suppression of plasma cortisol levels is achieved after dexamethasone administration, even at high doses. A paradoxical increase in urinary free cortisol levels after high-dose dexamethasone administration during the 6-day Liddle test may be considered the most characteristic sign (included in the diagnostic criteria). The test consists of basal measurements of urinary free cortisol for the first two days, measurement of urinary free cortisol after the administration of low glucocorticoid doses (0.5 mg/6 h in adults or 7.2 µg/kg/6 h in children) for the next two days, and measurements after administration of high glucocorticoid doses (2 mg/6 h in adults and 28.5 µg/kg in children) on days 5 and 6. This test allows for differentiating PPNAD from all other primary nodular adrenal diseases (adrenal adenoma, macronodular adrenal disease). A > 100% elevation in urinary cortisol levels on day 6 is diagnostic of PPNAD (false negative rate 61%), although a > 50% elevation occurrs in 69% of PPNAD as compared to only 20% of single adenomas and 0% of bilateral macronodular hyperplasias. This test is highly useful for PPNAD diagnosis in the subgroup of patients with

a discrepancy between ACTH levels and urinary free cortisol levels[9].

Subsequent studies suggest that this characteristic differentiating PPNAD is due to a direct effect of glucocorticoids upon the adrenal glands and to the higher number of glucocorticoid receptors in these as compared to normal adrenal glands[10,11].

Imaging tests
In PPNAD, adrenal glands have a normal size and weight. Adrenal glands may therefore appear normal in computed tomography (CT) in more than a third of patients. In all other patients, micronodules, or even macronodules in some cases, are seen in one or both adrenal glands. MRI does not improve the results of tomography. A typical radiographic bed and string image was initially described in PPNAD, but is currently considered to be non-specific.

A cholesterol iodine scan may also be useful for diagnosis because it usually shows bilateral adrenal uptake. However, this radiotracer is not marketed and so has not been used for studying PPNAD in recent years[8].

Pathology
On gross examination, adrenal glands show bilateral changes such as multiple small (< 4 mm) black, brown, dark green, or even red or yellow nodules, cortical atrophy, and structural disorganization.

Microscopically, the nodules consist of hyperplastic cortical cells with wide eosinophilic cytoplasm containing lipofuscin. They are positive for synaptophysin in immunohistochemistry.

It should be noted that autopsies in CNC patients have shown morphological changes characteristic of PPNAD in adrenal glands even when they had no signs of hypercortisolism. This suggests that PPNAD is a consistent manifestation in CNC, although with variable degrees of clinical expressivity[12].

Acromegaly
Clinically significant acromegaly secondary to GH-secreting adenomas occurs in 12% of CNC patients. Acromegaly in CNC is characterized by a slow, insidious course. Mean age at presentation is 35 years approximately[4].

Biochemical acromegaly (GH and IGF-1 elevation with mild hyperprolactinemia) may occur in up to 75% of patients with CNC. These biochemical changes are usually unmasked by the occurrence of abnormal results after an oral glucose tolerance test or a paradoxical response after the administration of TRH[13].

Patients with clinically active acromegaly usually show macroadenomas in imaging tests, as in non-familial cases, while imaging tests are generally negative in those with biochemical changes but no clinical signs.

It has been reported that in many patients with clinically significant acromegaly the disease did not become apparent until they underwent surgery for Cushing's syndrome. Seventy-two percent of patients have concomitant acromegaly and PPNAD.

Pathological findings in patients with CNC and acromegaly include hyperplasia of the pituitary cells secreting GH and prolactin. GH-secreting cells mark positivity for prolactin and other pituitary hormones. The presence of generalized hyperplasia of somatotropic cells in autopsies performed on patients with CNC accounts for the high prevalence of biochemical changes in acromegaly. Genetic testing of these lesions shows multiple changes which are proportional to the degree of clinical severity[14].

Thyroid gland
Thyroid gland involvement may range from benign nodular disease to differentiated thyroid carcinoma. Ultrasound examination reveals multinodular disease in up to 75% of patients. Twenty-five percent of patients have thyroid tumors (of which follicular adenoma is the most common), 2.5% of which are malignant in nature (follicular or papillary carcinoma). There is no increased risk of hypothyroidism or hyperthyroidism[15].

Gonads
Testicular tumors are found in 33% of CNC patients at diagnosis. Large-cell calcifying Sertoli cell tumors (LCCSCT) are found in virtually all cases, but Leydig cell tumors of residual adrenocortical tumors rarely occur. The vast majority are non-palpable benign tumors with a low malignant potential. These tumors are easily diagnosed by the presence of bilateral microcalcifications in ultrasound examination. LCCSCT may be hormonally active and cause gynecomastia in prepubertal and peripubertal males due to increased peripheral aromatase expression.

Ovarian cysts are frequently seen in ultrasound examination. They are usually non-clinically significant and benign, but ovarian adenocarcinoma may develop in exceptional cases[4,16].

Treatment
Treatment for CNC varies according to the clinical signs. Treatments of choice include:

- Cardiac myxoma: heart surgery.
- Cutaneous myxoma: resection.
- Cushing's syndrome: bilateral adrenalectomy.
- Pituitary adenoma: transsphenoidal surgery.
- Thyroid tumors: surgery if malignancy is suspected.
- LCCSCT: orchiectomy, particularly at a pubertal age and if gynecomastia exists.
- Psammomatous melanocytic schwannoma: surgery on primary and/or metastatic lesion.

Follow-up
Patients diagnosed with CNC should undergo diagnostic tests to detect other signs of the disease. These tests should be performed every year. Recommended tests include:

- Annual echocardiogram.
- Annual measurement of urinary free cortisol levels or Nugent's dexamethasone suppression test.
- Annual measurement of plasma IGF-1 levels.
- Annual thyroid ultrasonography.
- Annual testicular ultrasonography in males.
- Clinical monitoring of ductal adenoma of the breast.

Early detection of PPNAD or GH-secreting adenoma requires more complete and specific tests (6-day Liddle test for PPNAD and oral glucose tolerance test or TRH test for pituitary disease).

Genetics of Carney complex

CNC is genetically heterogeneous. Two different loci have been identified, one in the 17q22-24 region (CNC1) and the other in the 2p16 region (CNC2)[17,18]. The gene causing CNC1 has been identified as the regulatory subunit (R1A) of protein kinase A (PRKAR1A). The causative agent in CNC2 has not yet been found. Heterozygous inactivating mutations in the PRKAR1A gene, found in approximately 70% of patients, cause the disease. Thirty percent of patients have a *de novo* mutation, while the rest (70%) have relatives who are affected.

The PRKAR1A gene comprises 11 exons and results in a genomic region of approximately 21 kb, with a coding region of 1,143 base pairs (start at exon 2)[19-21].

The protein expressed by the PRKAR1A gene is one of the regulatory subunits of protein kinase A (PKA), a protein kinase dependent on cyclic AMP (cAMP) with a key role in the cell signaling process and related to endocrine tumorigenesis processes because it is implicated in a wide variety of cell processes, including transcription, metabolism, cell cycle progression, and apoptosis.

PKA is a key component of the cAMP signaling pathway. PKA is a holoenzyme consisting of a tetramer of two subunits, with three isoforms (C1, C2, C3) which are responsible for its catalytic activity, and two regulatory subunits having four isoforms (R1A, R1B, RIIA, RIIB) encoded by four genes (PRKAR1A, PRKAR1B, PRKAR2A, PRKAR2B). Depending on the combination of these subunits, PKA is classified as type I (a regulatory subunit consisting of an R1A or R1B dimer) and type II (a regulatory subunit consisting of an RIIA or RIIB dimer)[5]. The PRKAR1A gene therefore encodes the regulatory subunit R1A which is part of PKA. Both types of PKA are co-expressed in virtually all tissues, but their expression levels vary in the different tissues. PKA is inactive in its tetrameric form. The binding of cAMP to the two binding sites located at the regulatory subunits leads to the dissociation of the catalytic subunits from the regulatory subunits, which results in the active form of PKA. This active form is able to phosphorylate serine or threonine residues at membrane or cytoplasm level or, after the entry of the catalytic unit into the nucleus, at nuclear level. Nuclear phosphorylation of the ser-133 residue of CREB (c-AMP response element binding protein) causes the activation of the transcription factors and subsequent regulation of the expression of downstream genes with CRE (c-AMP response element)[22,23] (Fig. 1).

In the international series of Bertherat et al., 73% of patients with CNC had inactivating mutations of the PRKAR1A gene, and up to 80 different mutations were detected. Most mutations were single base pair substitutions or some exon insertions or deletions. A vast majority of them were frameshift mutations due to insertion, deletion, or a change affecting a base pair, while the rest were missense, nonsense, or splicing site mutations. These mutations may affect any gene region, but are most common in exons 2, 3, 5, 7, and 84.

Most of these mutations (82%) result in the appearance of a termination codon, which leads to an abnormal mRNA that causes the protein encoded by this gene to be shorter than usual (truncated protein). This abnormality is detected and recognized by nonsense mediated mRNA decay (NMD), which is activated by tissue cells when truncated protein codings that would prevent normal function are detected and results in the degradation of this mRNA[19]. This means that these mutations do not lead to the expression of a detectable abnormal protein (non-expressed mutations). Thus, the great majority of mutations have the same effect at molecular level: lack of a detectable mutated protein and a 50% reduction in protein R1A expression, because only the non-mutated allele will be able to express itself. This phenomenon, known as PRKAR1A gene haploinsufficiency (the inability of a single normal gene to maintain the normal phenotype in an individual), is considered to be responsible for CNC[19,23,24].

At the biochemical level, the 50% reduction in R1A causes a compensatory increase in the other components of the PKA tetramer, including type 1 (PRKAR1B) and type 2 (PRKAR2A and PRKAR2B) PKA subunits, depending on tissue, cell phase, and other factors. Such an increase results in elevated PKA activity (caused by the activity of uncontrolled catalytic subunits) and cell cycle abnormalities in both human and rodent cells[24]. To sum up, inactivation of the PRKAR1A gene is associated with increased PKA activity in certain tissues of an endocrine origin where it may stimulate cell proliferation resulting in the endocrine tumorigenesis characteristic of CNC[25].

Mutations in the PRKAR1A gene escaping NMD and expressing mutated proteins at cell level, inducing a more aggressive clinical expression due to a greater *in vitro* PKA activity have recently been reported[26,27]. Based on this, one is tempted to state that NMD activity exerts a protective role, preventing a greater clinical expressivity of CNC.

The fact that, despite the great number of mutations reported, a vast majority of them, by the mechanisms previously described, cause the same final effect would explain the apparent absence of any clinical differences between subjects with different mutations in PRKAR1A and the apparent lack of a genotype-phenotype correlation. Over the years, some connections have been found between genotype and phenotype despite the inherent heterogeneity of CNC, even in patients who have not escaped the degradation cascade. The most noteworthy of these are the presence of the c.709_7del6 mutation in patients with isolated PPNAD, the c.491_492del TG mutation (cardiac myxomas, lentiginosis, and thyroid tumors), and the more common occurrence of myxoma, thyroid tumors, TGCGS, and schwannoma in patients carrying mutations in the PRKAR1A gene as compared to non-carriers. It is interesting to note that the c.491_492del TG mutation, seen in several unrelated families, is the most commonly reported mutation[4].

The determination of inactivating mutations in the type 1A (R1A) regulatory subunit of the PKA gene (PRKAR1A) in most patients with CNC has made it possible to estimate its penetrance, validating diagnostic criteria for the disease,
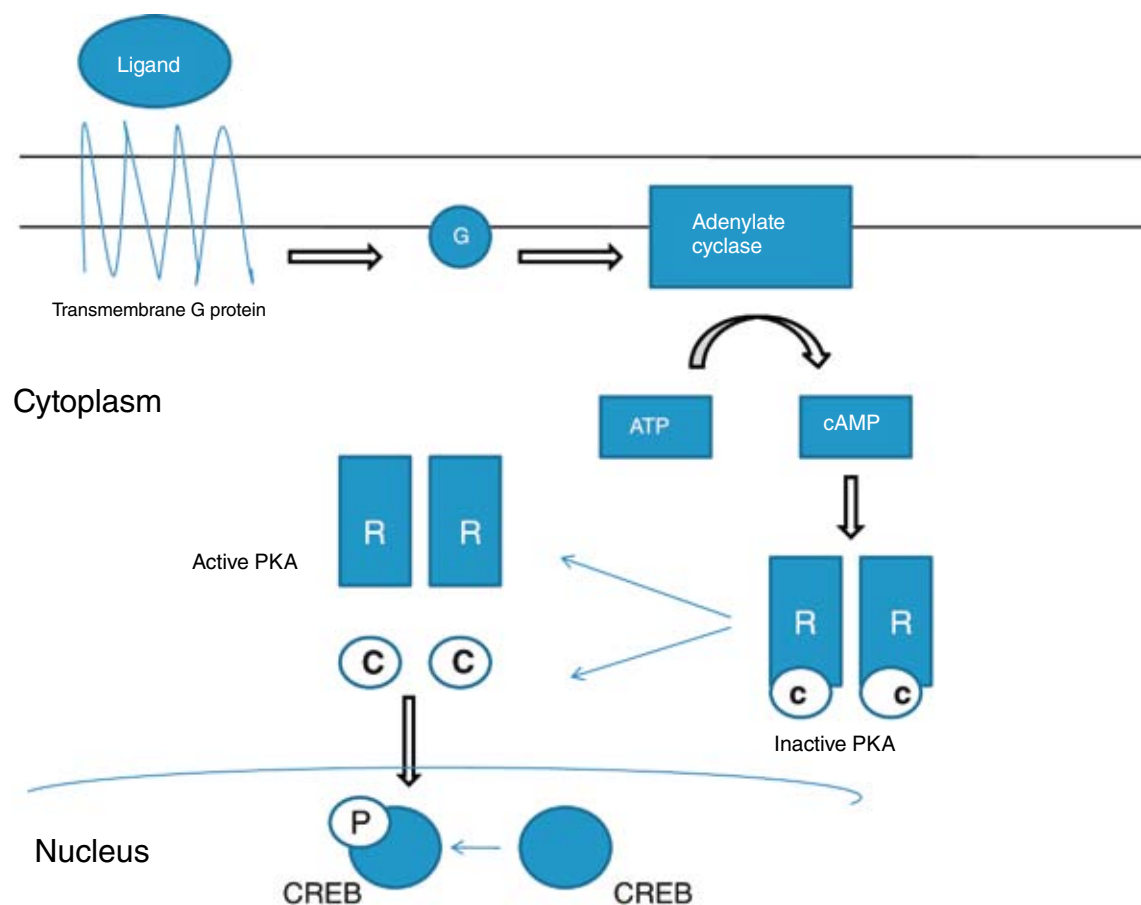
Figure 1 Ligand binds to transmembrane G protein, activating stimulation of G protein (G). This interacts with adenylate cyclase, allowing for cAMP accumulation in cytoplasm. cAMP enters into contact with inactive protein kinase A (PKA), which allows for activation and release of catalytic subunits (C). These catalytic subunits are able to phosphorylate serine and threonine residues in membrane, cytoplasm, or nucleus. One of these PKA phosphorylation targets is CREB (cAMP response element-binding), located in the nucleus, which allows for transcription activation.

and showing that no clear phenotype-genotype correlation exists.

Genetic counseling

Genetic testing to assess the presence of inactivating mutations should be proposed to all index cases. If a mutation is detected in the PRKAR1A gene, genetic testing should be proposed to all first-degree relatives. This would allow for early diagnosis and for the performing of tests to search for other manifestations of CNC in carrier patients. It would also prevent unnecessary tests being given to non-carrier relatives, with a resultant reduction in both healthcare costs and anxiety in these subjects[28,29].

Conflict of interest

The authors state that they have no conflict of interest.

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