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Clinical and genetic aspects of cardiac myxomas

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Primary cardiac tumors are rare and occur in 1 per 1000 to 1 per 100,000 individuals in unselected autopsy series at tertiary care centers.[1] Among these tumors, cardiac myxomas are the most common in adults, accounting for nearly half of primary cardiac tumors. For many years, the cellularity of these lesions was controversial and some investigators initially proposed that they represented thrombus rather than neoplasia. However, extensive analysis ultimately confirmed that these lesions represented a primary neoplastic process.[1,2] Although the cell of origin has yet to be isolated, they have been posited to arise from a subendocardial cell, termed a "reserve" or "lepidic" cell. These tumors usually exhibit a typical hypocellular appearance of small pyramidal or stellate cells against a bland proteoglycan background. They may also exhibit evidence of a wide variety of cellular lineages, including zones of extramedullary hematopoiesis, acinar structures suggestive of epithelial organization, cells with electron microscopic features suggestive of muscle, and a number of immunohistochemical markers consistent with a remarkable range of cell types. Such histologic studies[1-3] suggest that the cardiac reserve cell is pluripotent and, in the appropriate genetic and biochemical milieu, may be a progenitor cell for a number of cardiac cells in the healthy and pathologic heart.

Cardiac myxomas are most commonly located at the *fossa ovalis* on the left side of the interatrial septum and exhibit a strong preference for women aged 40-60.[4] Patients often present with a classic triad of symptoms: heart failure due to obstruction, stroke due to embolism, and constitutional, rheumatologic symptoms thought to be due to tumor secretion of cytokines such as interleukin-6. If detected prior to embolism, cardiac myxomas are usually highly amenable to surgical resection since they are non-metastatic lesions. Both heart failure and constitutional symptoms usually resolve following surgical resection.

At least 7% of patients[5,6] with cardiac myxomas account for a distinct subpopulation that exhibits a familial pattern of disease and, in whom, cardiac myxomas appear to be only one component of a more complex neoplastic syndrome. First described by Rees and colleagues in 1973,[7] this syndromic form of cardiac myxoma has been referred to[8-10] by a number of names including: syndroma myxoma, Swiss syndrome, NAME (Nevi, Atrial myxoma, Myxoid neurofibromata, Ephelides), and LAMB (Lentigines, Atrial myxoma, Mucocutaneous myxoma Blue Nevi).

In further clinical studies that prompted the nomenclature Carney complex for the disorder, Carney[5,6] demonstrated that cardiac myxomas arise in patients with this familial disorder in the setting of spotty pigmentation of the skin (including lentigines, ephelides and blue nevi), cuta-

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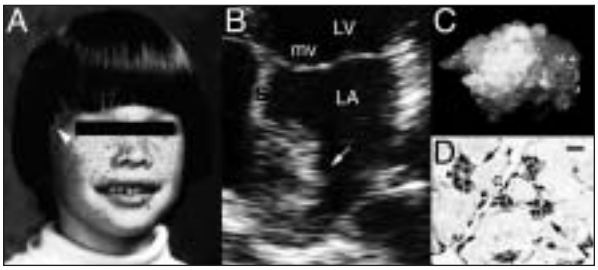
Figure 1. Typical clinical features of Carney complex.



Examples of cutaneous (A) and cardiac (B-D) manifestations of Carney complex in three individuals from one family with Carney complex. (A) One individual exhibits the typical spotty pigmentation and lentiginosis of Carney complex. Note the hyperpigmentation of the lips as well as the large nevus on this individual's right temple (arrowhead). Later in life, this individual also developed recurrent intracardiac myxomas. (B) Echocardiographic view a related individual's left atrium (LA) bordered by the mitral valve (mv) below the left ventricle (LV) and the interatrial septum (s). Note the large mass (atrial myxoma; arrow) arising from the interatrial septum. This individual also exhibits lentiginosis similar to her cousin (presented in panel A), and has also required resection of a cutaneous myxoma. (C) A third individual in this same family, who also has typical hyperpigmentation and lentiginosis, required resection of this left atrial intracardiac mass after developing symptoms of an embolic stroke. (D) Histopathologic analysis (hematoxylin and eosin stain) of the mass shown in panel C reveals typical stellate myxoma cells (arrows) surrounded by abundant extracellular matrix and a capillary (c) coursing through the field. [Bar = 30 mm] (Reprinted with permission from Casey et al. *Circulation* 1998;98:2560-66.)

neous myxomas, nonmyxomatous extracardiac tumors (eg, pituitary adenomas, Sertoli cell tumors, psammomatous melanotic schwannomas, and breast fibroadenomas), and hyperendocrine states. Although endocrinopathy can reflect dysfunction of almost any endocrine organ, of particular note, is the unusual form of Cushing syndrome due to primary pigmented nodular adrenocortical disease.

Clinical presentation

Although the cardiac myxomas of Carney complex are histologically indistinguishable from nonsyndromic cardiac myxomas, their clinical presentations and significance are quite distinct (Figure 1). In addition to the associated noncardiac manifestations, Carney complex cardiac myxomas may exhibit unusual atrial as well as ventricular locations, affect a broader demographic group of patients, and have a unique response to therapy. Although Carney complex myxomas still exhibit a predilection for the left atrial aspect of the *fossa ovalis*, more than one-third of these tumors occur at other anatomic locations in the heart. They may occur in either of the ventricles or the atria and may arise from either free walls or septa. Carney complex shows no age or gender preference, although development of cardiac myxomas in the preadolescent child is rare. Most important for the clinician is the recognition that despite adequate surgical resections, cardiac myxomas can recur in Carney complex patients at locations at, near, or remote from the initial operative site. Some individuals have had more than 5 recurrences in their lifetimes.

Thus, the observation that a patient with a cardiac myxoma has a family history of cardiac myxoma, a past medical history of a cardiac myxoma, a history of noncardiac myxomas or unusual forms of other tumors (eg, schwannomas or Sertoli cell tumors), endocrinopathy, and/or spotty pigmentation of the skin should raise the index of suspicion that such a patient's tumor is part of a broader syndrome. This patient not only needs definitive therapy from surgical resection, but also requires lifelong annual surveillance echocardiography to detect intracardiac tumor recurrence. The recognition of spotty pigmentation of the skin is particular critical in establishing this diagnosis, since unlike the other disease manifestations that are variably present, cutaneous manifestations are present in nearly all individuals with Carney complex. In "classic" cases, the spotty pigmentation takes the form of extensive facial (particularly infraorbital and perioral) lentigines and ephelides. However, some patients exhibit scant evidence of spotty pigmentation or may have only a single lesion that is notable solely for its unusual location, (ie, the vermilion borders of the lips, corneas, and mucosal membranes of the mouth, anus and genitalia).

Disease gene identification

The early recognition that Carney complex is inherited in families as an autosomal dominant disorder suggested that the disease might be amenable to genetic linkage analysis to identify the disease-causing defective gene. Initial genetic analyses by Stratakis[11] focused on a group of small families and suggested evidence of linkage to chromosome 2p. However, no single family exhibited statistically significant evidence of linkage to this locus, and only by aggregating low, insignificant LOD scores, were these investigators able to derive data with a trend toward linkage at this locus. We subsequently analyzed a large family with Carney complex[12] and showed that disease in this kindred could not be explained by a chromosome 2p gene defect. Our random gene search[13] then revealed a highly statistically significant chromosomal locus (odds in favor of linkage of approximately 1,000,000:1) on chromosome 17q2 that contained a gene defect for Carney complex. Further genetic linkage studies[13] of several other families, including one Stratakis[11] originally concluded was linked to chromosome 2p, demonstrated that Carney complex in all of these families was caused by a gene defect at this chromosome 17q2 locus. Thus, modern genomics pro-

vided clear evidence that a mutated gene at chromosome 17q2 causes Carney complex.

Establishment of a major locus for Carney complex at chromosome 17q2 then set the stage for identification of the specific disease gene associated with this disorder.[14] We utilized a positional-candidate gene approach. Haplotype analyses of several Carney complex families linked to chromosome 17q2 produced a minimal genomic interval of approximately 12 million basepairs of DNA containing the disease gene. With the assistance of physical maps, established by the Human Genome Project, we were able to clone this chromosome 17q2 interval.[14] Examination of the genes located within the locus revealed the presence of several genes that might be associated with tumorigenesis. One of these genes, *PRKAR*1α, encoded the R1α regulatory subunit of protein kinase A (PKA). The locus containing this gene had previously been referred to as TSE, "Tissue-Specific Extinguisher," and deletion of this locus had been demonstrated to alter several cell functions.[15-17] Moreover, mutations in another gene encoding a different kinase, STK11, had been shown to cause Peutz-Jeghers syndrome, which is characterized by lentiginosis similar to that seen in Carney complex, as well as by tumors of the gastrointestinal tract.[18] Thus, *PRKAR*1α seemed an ideal candidate disease gene for Carney complex.

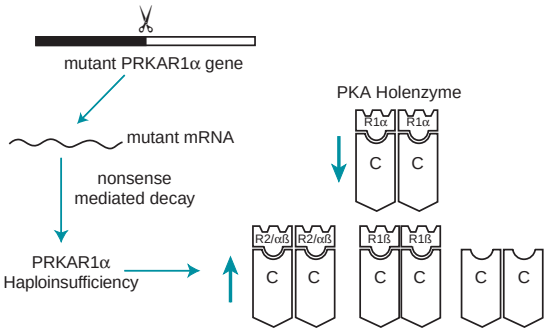
Advances in the Human Genome Project significantly accelerated consequent mutational analysis of the *PRKAR*1α gene in patients with Carney complex. Although previous studies of this gene had erroneously assessed the number of exons and introns in the *PRKAR*1α, the gene's true genomic structure[14] was rapidly and easily elucidated by comparing the known nucleotide sequence of the gene's coding region with the Human Genome Project's sequence of the chromosome 17q24 region of the genome. Bioinformatic analysis rapidly determined that the gene is comprised of 11 exons, and permitted the establishment of primer pairs for their individual amplification from genomic DNA samples isolated from the peripheral blood of patient's with Carney complex. The amplified exons could be sequenced or subjected to denaturing HPLC analyses to look for sequence variants. These studies demonstrated that mutations in *PRKAR*1α do, in fact, cause Carney complex.[14,19] Similar studies by others[20,21] have confirmed this conclusion. Mutations have been identified in all exons of *PRKAR*1α, and our studies[14,19,22] have demonstrated that these mutations occur in individuals descended from a wide variety of ethnic and racial backgrounds, including caucasian, black, hispanic, and asian. We have identified *PRKAR*1α mutations in approximately two-thirds of patients with Carney complex. In addition, our retrospective clinical and *PRKAR*1α genetic analyses suggest that previous estimates of the fraction of cardiac myxoma patients that fall into the Carney complex may be significant underestimates; more than one-quarter of cardiac myxomas patients may fall into this clinical and genetically-determined category (M. Veugelers, C.T. Basson, unpublished data).

PKA and cardiac myxomas

*PRKAR*1α Carney complex mutations generally include nonsense mutations, as well as frameshift mutations, that result from insertions, deletions, and alterations in intronic sequences that modulate *PRKAR*1α mRNA splicing. All such mutations lead to abnormal mRNA isoforms which, evidence suggests, are recognized and degraded by the cell via a biochemical pathway referred to as nonsense-mediated decay (NMD). NMD is a regulatory system triggered by DNA mutations that would lead to truncated proteins that would interfere with abnormal cell function if the usual DNA transcription to RNA and RNA translation to protein occurred. Therefore, the cell activates a series of RNA degrading enzymes to destroy the mutant mRNA before it can encode protein. Since individuals with autosomal dominant Carney complex are heterozygous for *PRKAR*1α mutations – that is, of an affected individual's two *PRKAR*1α gene alleles, one is normal and the other mutant – the result of NMD is a halving of *PRKAR*1α protein since only the normal, but not the mutant *PRKAR*1α allele, will encode protein. Such a genetic halving of protein is referred to as haploinsufficiency. *PRKAR*1α haploinsufficiency is thought to be the cause of most cases of Carney complex (Figure 2).

How might alterations in R1α protein levels, mediated via *PRKAR*1α gene haploinsufficiency, cause cardiac myxomas and Carney complex? To appreciate the significance of *PRKAR*1α haploinsufficiency, it is critical to understand the fundamental physiologic requirement for PKA activity. cAMP-dependent PKA is known to be a critical enzyme in intracellular signal transduction that regulates all aspects of cell metabolism.[23] This enzyme exists in the cell as an inactive tetramer comprised of 2 catalytic subunits and 2 regulatory subunits. There are 2 genes for catalytic subunits (Cα and Cß) and 4 genes for regulatory subunits (R1α, R1ß, RIIα, and RIIß). cAMP binds to the regulatory subunits and stimulates their dissociation as a dimer from the catalytic subunits. Free catalytic subunits of the kinase exist then as monomers and are active to phosphorylate target proteins within the cell. The array of phosphorylation targets for PKA is vast and touches on every aspect of cellular function and homeostasis. These include membrane receptors, cytoskeletal proteins including intermediate filaments and sarcomeric proteins, small neurotransmitters (eg, acetylcholine, dopamine, and norep-

Figure 2. Molecular consequences of PRKAR1a mutation in Carney complex.



In approximately 2/3 of patients with Carney complex, disease is caused by heterozygous "truncating" mutations (frameshift and nonsense) in the PRKAR1a gene. The mutant allele encodes an abnormal RNA which is recognized by the cell and then degraded via nonsense mediated decay. The consequence is a 50% reduction in gene dose referred to as haploinsufficiency. PRKAR1a haploinsufficiency results in decreased expression of the R1a regulatory subunit of protein kinase A (PKA) and an altered ratio of PKA holoenzyme isoforms with relatively increased amounts of active free catalytic subunit (C) or catalytic subunits associated with other regulatory subunits. These biochemical changes produce changes in PKA activity and PKA effects on cell proliferation and differentiation that the set the stage for further acquired somatic mutation in PRKAR1a or other genes that finally initiates cardiac tumorigenesis.

inephrine), peptide hormones (eg, vasoactive intestinal peptide and growth hormone releasing peptide), and other enzymes (eg, glycogen phosphorylase). Thus, cellular activities, including proliferation, differentiation, migration, contraction, secretion, and hormonal responsiveness, are all regulated by cAMP and protein kinase A. The key PKA activities in the heart that are modified and result in the specific Carney complex phenotype remain unknown and are the targets of active investigation in human and animal model systems in our laboratory.

Both an overall change in PKA activity and changes in PKA regulatory subunit isoform balance appear to play a role in the development of disease in Carney complex. As previously mentioned, *PRKAR*1α haploinsufficiency leads to decreased levels of R1α protein. The consequences of decreased R1α levels have now been studied in endocrine and cardiac tumor cells. Kirschner et al[20,21] studied cultured cells from endocrine tumors resected from individuals with Carney complex or without Carney complex. Although basal levels of PKA activity did not differ in these two sets of endocrine tumors, these investigators did observe a marked reduction in cAMP ability to stimulate PKA activity in the Carney complex tumors that were haploinsufficient for R1α. Such reduced ability of cAMP to stimulate PKA activity may not solely be a consequence of decreased regulatory subunit levels, since data from murine knockout models[24] suggest that changes in one regulatory subunit may result in compensatory changes in another subunit. We have investigated such alteration in regulatory subunit isoform balance in cardiac myxomas. Intriguingly, we observed that loss of R1α in these heart tumors is associated with increased levels of RIIß.[14,22] Thus, altered PKA activity may actually reflect a change in PKA tetramer composition rather than simply a reduction in regulatory subunit levels. Such a hypothesis is supported by the observation that Carney complex patients often exhibit lipomatous hypertrophy of the interatrial septum at a young age. In the mouse, knockout of the RIIß PKA regulatory subunit produces a compensatory increase in R1α that causes increased lipolysis and a lean animal.[24] It is conceivable then that the converse situation in human patients with Carney complex (ie, decreased R1α with a compensatory increase in RIIß) may actually be associated with increased fat synthesis/deposition and thereby result in lipomatous hypertrophy in the heart.

How, then, might these data add up to a pathway to cardiac tumorigenesis? Individuals with Carney complex are heterozygous for mutations in *PRKAR*1α that lead to R1α haploinsufficiency. Loss of R1α leads to altered regulatory subunit balance and decreased ability of cAMP to stimulate PKA activity. Dysregulated cellular homeostatic mechanisms, secondary to cAMP insensitivity, can lead to several abnormal proliferation and differentiation events depending on the effected cell type. In the skin and adrenal gland, the result may be hyperfunctioning melanocytes and endocrine secretory cells with consequent hyperpigmentation and endocrine overactivity. In some cases, R1α may act as a classic tumor suppressor gene. Thus, in cells such as subendocardial cardiac reserve cells, loss of R1α may set the stage for increased proliferation. This predisposing insult may act as the first "hit" in a tumorigenic cascade per Knudsen's two hit hypothesis. Mutant cells may be subjected to higher levels of metabolic stress and therefore be more susceptible to acquired somatic mutation of other tumor suppressor genes to create the second "hit" that triggers neoplastic growth. Although Kirschner et al[20] have suggested that such a second hit

may actually be somatic mutation of the wildtype *PRKAR*1α allele in patients with Carney complex (who are heterozygous for a constitutional mutation in one *PRKAR*1α allele), our data[14,22] suggest that loss of *PRKAR*1α heterozygosity or other mutation of the wildtype allele is rare in cardiac myxomas. Thus, if a second "hit" is required for the initiation of cardiac neoplasia, it likely reflects mutation of genes distinct from *PRKAR*1α.

Cytogenetic analyses of cardiac myxomas have documented a wide array of chromosomal aberrations affecting loci other than the chromosome 17q2 *PRKAR*1α locus, and all of these contain candidate genes that may be involved in cardiac tumorigenesis and will be a focus of future investigation. Such genes are also candidate disease genes that may have primary constitutional mutations that cause Carney complex in the one-third of patients with this disorder who do not have any familial abnormality of the *PRKAR*1α gene.

Summary

Although much work remains to decipher all the details of the genesis of cardiac myxomas and the recent studies described here only define first glimpses into one inciting genetic event, these findings do set the stage for improving the care of our patients with cardiac myxomas and with cardiomyopathies. Already, we have been able to use genetic testing to identify individuals without prior clinical diagnoses of Carney complex, but who have *PRKAR*1α mutations and are therefore at risk for cardiac myxomas.[25] Such individuals are now undergoing annual surveillance echocardiography to detect cardiac myxomas and prompt surgical resection before they suffer the ravages of tumor embolism and stroke.

At the present time, individuals who present with an intracardiac myxoma should be carefully questioned regarding family history and evaluated for any clinical signs of a complex syndrome, including unusual spotty pigmentation (location or quantity), history of hyperendocrine states, cutaneous mxyomas, unusual tumors (eg, schwannomas, Sertoli cell tumors). If the any of these are present, if the patient's myxoma is in an unusual non-left atrial *fossa ovalis* location, or if the patient is young or male, the patient should be assumed to have a diagnosis of Carney complex. Such a patient requires exclusion of endocrinopathy prior to undergoing cardiac surgery and will require surveillance echocardiography. Research protocol based genetic testing (ie, *PRKAR*1α DNA analysis) is currently available in our laboratory and may be helpful in clarifying difficult diagnoses. Because the disorder is transmitted in families in an autosomal dominant pattern, first-degree relatives of affected individuals have a 50% risk of also being affected, but may not yet have manifested clear signs or symptoms of the disease. Thus, genetic testing may be particularly useful for counseling first-degree relatives of an affected individual. Prenatal diagnosis via DNA testing, although feasible, is unlikely to be of benefit except if preimplantation diagnosis in the context of *in vitro* fertilization using the gametes of an affected individual is a consideration. These are complex medical and social issues and all discussion of such inherited cardiovascular disease should occur in the setting of both cardiology and genetics subspecialists so the patient can receive optimal counseling. Our laboratory welcomes contacts from patients and their physicians to review the genetic aspects of Carney complex and the current state of DNA-based genetic testing.

In the future, we anticipate that the definition of the biochemical pathways that are genetically altered in patients with Carney complex will suggest pharmacogenomic therapeutic targets in patients with familial and sporadic cardiac myxomas. Such therapies may well obviate the need for surgery, not only by preventing tumor recurrences, but also by providing medical therapies to treat initial tumor occurrences. However, it is likely that these scientific endeavors will have implications not only for cardiac myxoma patients, but also for individuals with common ischemic and non-ischemic cardiomyopathies. The recognition that cardiac myxomas arise from pluripotent stem cells in the heart, coupled with recent observations that some cardiomyocytes can undergo mitosis in response to myocardial infarction, provides hope that someday cardiologists will be able to use pharmacogenomic approaches to stimulate myocardial regeneration in individuals with heart failure.

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