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GENETIC DISORDERS ASSOCIATED WITH CARDIAC MYXOMAS

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ABSTRACT
Cardiac myxomas are the most common primary benign tumors of the heart, accounting for approximately 50–80% of all primary cardiac neoplasms. Although most cardiac myxomas occur sporadically, approximately 7–10% are associated with inherited genetic disorders, most notably Carney complex (CNC), an autosomal dominant multiple neoplasia syndrome caused primarily by pathogenic variants in the PRKAR1A gene. Familial cardiac myxomas differ significantly from sporadic tumors in terms of age of onset, recurrence rate, multiplicity, and anatomical distribution, highlighting the importance of recognizing hereditary syndromes in affected patients. Advances in molecular genetics have revealed that dysregulation of cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA) signaling represents the principal mechanism underlying hereditary cardiac myxoma development. Additional molecular pathways involving Wnt/β-catenin signaling, inflammatory cytokines, angiogenesis, and epigenetic regulation have also been implicated in tumor progression. Genetic testing has become an essential component of the diagnostic evaluation of patients with recurrent, multifocal, or early-onset cardiac myxomas, facilitating surveillance of at-risk relatives and early detection of associated endocrine and extracardiac neoplasms. This review summarizes the current understanding of the genetic disorders associated with cardiac myxomas, emphasizing the molecular basis of tumorigenesis, genotype–phenotype correlations, clinical manifestations, and implications for diagnosis, genetic counseling, and long-term surveillance.
KEYWORDS: Primary cardiac tumors ; Carney complex; PRKAR1A; familial cardiac tumors; myxoma genetics disorders.

INTRODUCTION

Cardiac myxomas are the most common primary benign tumors of the heart, accounting for approximately 50–80% of all primary cardiac neoplasms. They are usually sporadic, arising predominantly in the left atrium, with a higher incidence among women. Despite their benign histological characteristics, cardiac myxomas can produce severe clinical complications, including intracardiac obstruction, systemic embolization, neurological events, arrhythmias, constitutional inflammatory symptoms, and sudden cardiac death [1,2].

The majority of cardiac myxomas occur sporadically; however, approximately 7–10% are associated with familial disease or inherited genetic syndromes. Familial cardiac myxomas differ significantly from sporadic tumors by presenting at a younger age, involving multiple cardiac chambers, occurring in multiple family members, and demonstrating a higher recurrence rate after surgical excision [3,4]. These differences suggest that hereditary forms represent a distinct biological entity driven by underlying genetic alterations rather than isolated tumor development.

The most important inherited disorder associated with cardiac myxomas is Carney complex (CNC), an autosomal dominant multiple neoplasia syndrome characterized by cardiac myxomas, endocrine tumors, skin pigmentation abnormalities, and other benign or malignant neoplasms. The identification of pathogenic variants in the PRKAR1A gene was a major breakthrough in understanding the molecular mechanisms of hereditary cardiac myxoma formation and established abnormalities in cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA) signaling as a central mechanism of tumorigenesis [5,6].

Increasing evidence indicates that cardiac myxoma development involves complex interactions between inherited genetic susceptibility, altered intracellular signaling pathways, inflammatory responses, angiogenesis, and changes in extracellular matrix regulation. Understanding these molecular mechanisms has important clinical implications because genetic diagnosis allows early identification of affected individuals and implementation of surveillance strategies for patients and their relatives.

Molecular Genetics of Cardiac Myxomas

PRKAR1A: The Major Susceptibility Gene

The discovery of PRKAR1A mutations in patients with Carney complex represented a fundamental advance in hereditary cardiac tumor research. The PRKAR1A gene is located on chromosome 17q24.2 and encodes the regulatory subunit type I-alpha (RIα) of protein kinase A (PKA), a critical mediator of intracellular signaling induced by cAMP [7].

Under normal physiological conditions, PKA exists as an inactive tetramer composed of two regulatory and two catalytic subunits. Binding of cAMP to the regulatory subunits induces conformational changes that release the catalytic subunits, allowing phosphorylation of downstream targets involved in cellular metabolism, differentiation, proliferation, and gene transcription [8].

Pathogenic variants affecting PRKAR1A disrupt this regulatory mechanism. Most mutations are nonsense, frameshift, or splice-site variants that produce premature termination codons and lead to degradation of abnormal messenger RNA through nonsense-mediated decay. The resulting reduction in RIα protein causes excessive activation of PKA signaling, even in the absence of normal hormonal stimulation [7,9].

Unlike many classical tumor suppressor genes, complete loss of the second allele is not consistently observed in Carney complex-associated tumors. This suggests that haploinsufficiency, rather than a traditional two-hit mechanism, plays a major role in tumor development. Reduced PRKAR1A expression appears sufficient to alter cellular signaling, promote abnormal proliferation, and impair normal differentiation of susceptible mesenchymal cells [9,10].

cAMP/PKA Signaling and Tumor Development

The cAMP/PKA pathway regulates multiple cellular processes involved in growth control and differentiation. Excessive PKA activation resulting from PRKAR1A deficiency leads to abnormal phosphorylation of transcription factors, including the cAMP response element-binding protein (CREB), which regulates genes involved in cell survival and proliferation [8].

Experimental models have confirmed the importance of PRKAR1A in cardiac development and tumor suppression. Mice with reduced or absent Prkar1a expression develop abnormalities resembling features of Carney complex, including increased cellular proliferation and tumor formation in several tissues [10]. These models demonstrate that disruption of PKA regulation affects not only tumor growth but also normal differentiation pathways during development.

The cellular origin of cardiac myxomas remains incompletely understood. Current evidence suggests that they arise from multipotent mesenchymal progenitor cells within the endocardium. Abnormal PKA signaling may interfere with the differentiation of these cells, causing persistence of a primitive myxomatous phenotype characterized by production of abundant extracellular matrix and abnormal vascular structures [11].

Additional Molecular Pathways Involved in Cardiac Myxoma Formation

Although PRKAR1A dysfunction represents the primary genetic event in hereditary cardiac myxomas, additional molecular mechanisms contribute to tumor development and clinical behavior.

Inflammatory Pathways

Cardiac myxomas are biologically active tumors capable of producing inflammatory mediators, particularly interleukin-6 (IL-6). Increased IL-6 production explains many systemic manifestations, including fever, fatigue, weight loss, anemia, elevated erythrocyte sedimentation rate, and increased C-reactive protein levels [12].

IL-6 may also contribute directly to tumor progression through autocrine and paracrine signaling mechanisms. Elevated IL-6 levels correlate with tumor size and decrease rapidly after surgical removal, suggesting that IL-6 may serve as both a biomarker of disease activity and an indicator of tumor burden [12,13].

Other inflammatory mediators, including interleukin-8 and tumor necrosis factor-related pathways, have also been investigated, although their precise contribution to tumor initiation remains unclear.

Angiogenesis and Extracellular Matrix Remodeling

Cardiac myxomas are characterized histologically by abundant vascular channels embedded within a gelatinous extracellular matrix. This feature reflects increased activity of angiogenic and matrix-remodeling pathways.

Studies have demonstrated increased expression of vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and matrix metalloproteinases within cardiac myxoma tissue [11,14]. These molecules promote endothelial proliferation, extracellular matrix degradation, and tumor vascularization.

Matrix metalloproteinase activity may contribute to tumor mobility and embolic potential by weakening the structural integrity of the tumor. This mechanism may partly explain why even histologically benign cardiac myxomas can produce life-threatening complications.

Emerging Genetic and Epigenetic Mechanisms

Recent genomic studies have expanded understanding of cardiac myxoma biology beyond PRKAR1A abnormalities. Transcriptomic analyses have identified alterations in pathways involved in cell adhesion, extracellular matrix organization, angiogenesis, and mesenchymal differentiation [15].

The Wnt/β-catenin pathway has received particular attention because of its role in regulating stem-cell maintenance and cellular proliferation. Abnormal activation of β-catenin signaling has been reported in subsets of cardiac myxomas, suggesting possible interaction between Wnt signaling and PKA-mediated pathways [16].

MicroRNAs and epigenetic regulation are also emerging areas of investigation. Altered microRNA expression may influence angiogenesis, apoptosis, and extracellular matrix production, while abnormal DNA methylation patterns may contribute to changes in gene expression during tumor development [15,17].

However, because hereditary cardiac myxomas are rare, large-scale genomic studies remain limited. Future investigations using whole-exome sequencing, whole-genome sequencing, and single-cell molecular approaches are expected to identify additional susceptibility genes and clarify the mechanisms responsible for tumor initiation and recurrence.

Genetic Heterogeneity Beyond PRKAR1A

Although PRKAR1A mutations account for the majority of genetically confirmed Carney complex cases, approximately one-third of patients with a clinical diagnosis do not have identifiable pathogenic variants in this gene [6,18]. This observation suggests additional genetic mechanisms remain undiscovered.

Candidate genes involved in cAMP metabolism and signaling, including PRKACA, PRKACB, PDE11A, and PDE8B, have been investigated because of their roles in regulating PKA activity. However, their contribution to isolated familial cardiac myxoma development remains less established compared with PRKAR1A [18].

Familial cardiac myxomas without Carney complex features represent an important area of ongoing research. These families demonstrate clear hereditary transmission but lack endocrine and pigmentary manifestations, suggesting the existence of additional genetic syndromes yet to be fully characterized.

Carney Complex: Clinical Phenotype and Cardiac Manifestations

Carney complex (CNC) is the best-characterized hereditary disorder associated with cardiac myxomas. It is an autosomal dominant syndrome with variable expression caused predominantly by pathogenic variants in PRKAR1A. Since its original description by Carney and colleagues, CNC has been recognized as a multisystem neoplasia syndrome involving cardiac, endocrine, cutaneous, and neural tissues [5,6].

Cardiac myxomas represent one of the most clinically important manifestations of CNC because they are responsible for substantial morbidity and mortality. In contrast to sporadic cardiac myxomas, which usually occur as isolated tumors in the left atrium of middle-aged adults, CNC-associated myxomas frequently develop during childhood, adolescence, or early adulthood and may involve any cardiac chamber [6,19].

A major characteristic of hereditary cardiac myxomas is their tendency to be multiple, multicentric, and recurrent. Patients with CNC may develop tumors in different chambers either simultaneously or sequentially throughout life. Recurrence is believed to result mainly from the formation of new primary tumors rather than incomplete surgical removal, reflecting the persistent molecular abnormality present in all susceptible tissues [19,20].

The clinical presentation depends on tumor location, size, and mobility. Left-sided tumors may cause mitral valve obstruction, dyspnea, pulmonary edema, or systemic embolization. Right-sided tumors may produce right heart failure, pulmonary embolic events, or conduction abnormalities. In addition, inflammatory cytokine production may produce constitutional symptoms that mimic autoimmune or infectious diseases [12].

Because of these features, recognition of hereditary disease is essential whenever a cardiac myxoma occurs in a young patient, is recurrent, involves multiple chambers, or is associated with extracardiac manifestations.

Extracardiac Manifestations of Carney Complex

The diagnosis of Carney complex relies on the identification of characteristic clinical findings, which reflect the multisystem nature of the disease. Major manifestations include:

- Spotty skin pigmentation (lentigines and blue nevi)
- Cardiac myxomas
- Primary pigmented nodular adrenocortical disease (PPNAD)
- Growth hormone-producing pituitary adenomas
- Thyroid nodules and thyroid carcinoma
- Large-cell calcifying Sertoli cell tumors
- Psammomatous melanotic schwannomas [6,18]

Cutaneous manifestations are among the earliest and most recognizable signs of CNC. Lentigines typically appear during childhood and adolescence, often preceding the diagnosis of internal tumors. Their presence in a patient with cardiac myxoma should immediately raise suspicion for an inherited syndrome [6].

Endocrine abnormalities contribute significantly to morbidity. Primary pigmented nodular adrenocortical disease causes autonomous cortisol secretion and may lead to Cushing syndrome. Pituitary involvement may result in excessive growth hormone production and acromegaly, while testicular tumors may cause reproductive abnormalities in males [18].

The wide spectrum of manifestations explains why diagnosis is frequently delayed. Many patients first present with a cardiac event, while the dermatological or endocrine features may only be recognized retrospectively.

Genotype–Phenotype Correlations in PRKAR1A-Associated Disease

More than 150 pathogenic variants of PRKAR1A have been reported, including nonsense mutations, frameshift mutations, splice alterations, missense variants, and large genomic deletions [9,21]. Although the majority result in reduced expression of the RIα protein, predicting the clinical phenotype from the specific mutation remains challenging.

Some studies suggest that large deletions involving PRKAR1A are associated with earlier disease onset and more severe manifestations, whereas certain missense variants may produce milder or incomplete phenotypes [21,22]. However, substantial overlap exists between different mutation classes, and individuals carrying identical mutations may demonstrate very different clinical outcomes.

This variability indicates that additional modifying factors influence disease expression. Possible contributors include secondary genetic variants, epigenetic regulation, hormonal influences, and environmental factors. Therefore, molecular diagnosis should not replace clinical evaluation but should be integrated with family history, imaging findings, and multisystem assessment.

Familial Cardiac Myxomas Without Carney Complex

Although Carney complex represents the principal inherited syndrome associated with cardiac myxomas, some families demonstrate recurrent cardiac myxomas without the typical endocrine or cutaneous manifestations of CNC [3,23].

These cases, often referred to as familial isolated cardiac myxomas, usually show autosomal dominant inheritance and share several characteristics with CNC-associated tumors:

- Young age at diagnosis
- Multiple affected family members
- Increased recurrence risk
- Multiple cardiac locations

However, genetic testing does not identify PRKAR1A mutations in many of these patients, suggesting additional susceptibility genes remain unidentified [23].

Linkage analyses have suggested a possible second susceptibility region on chromosome 2p16 (historically referred to as CNC2), although the causative gene has not been conclusively established [24]. Advances in next-generation sequencing may eventually reveal additional genes involved in hereditary cardiac tumor formation.

The existence of PRKAR1A-negative familial cases highlights the complexity of cardiac myxoma genetics and suggests that the disease spectrum is broader than currently recognized.

Genetic Testing and Family Screening

The identification of hereditary cardiac myxomas has important implications for both patients and relatives. Genetic evaluation should be considered in patients with:

- Cardiac myxoma diagnosed before 40 years of age
- Multiple or recurrent cardiac myxomas
- Tumors involving unusual cardiac locations
- Family history of cardiac myxoma or Carney complex
- Associated pigmentation or endocrine abnormalities [6,18]

Molecular testing generally begins with sequencing of PRKAR1A, including deletion and duplication analysis when sequencing is negative. Identification of a pathogenic variant confirms the diagnosis and allows targeted testing of relatives.

Because CNC follows an autosomal dominant inheritance pattern, first-degree relatives of affected individuals have a 50% chance of carrying the mutation. Predictive testing allows identification of asymptomatic carriers who require lifelong surveillance [18].

Genetic counseling is essential because detection of a pathogenic variant has psychological, reproductive, and medical consequences. Counseling should include discussion of inheritance patterns, limitations of testing, possible uncertain variants, and the importance of long-term follow-up.

Surveillance and Clinical Management

The management of hereditary cardiac myxomas differs substantially from that of sporadic tumors. Surgical excision remains the definitive treatment; however, surgery does not eliminate the risk of recurrence in patients with CNC.

Patients with confirmed or suspected Carney complex require lifelong surveillance. Current recommendations include:

- Regular transthoracic echocardiography for detection of new cardiac myxomas
- Endocrine evaluation for adrenal, pituitary, thyroid, and gonadal disease
- Dermatological examination for pigmentation abnormalities and cutaneous myxomas
- Genetic screening of first-degree relatives [6,18]

After removal of a cardiac myxoma, repeated echocardiographic evaluation is particularly important because recurrence may occur years or decades after initial surgery. Some experts recommend annual echocardiography in mutation carriers and more frequent monitoring following tumor resection [18].

Complete surgical excision remains challenging in patients with multiple tumors because lesions may be distributed throughout different chambers. Careful inspection of all cardiac structures during surgery is therefore recommended to reduce the likelihood of missed lesions [20].

Future Perspectives and Targeted Therapies

The molecular characterization of hereditary cardiac myxomas has created new opportunities for improved diagnosis and treatment. Current research focuses on identifying additional genetic causes, developing molecular biomarkers, and understanding pathways that may be therapeutically targeted.

Several potential biomarkers are under investigation, including circulating microRNAs, inflammatory cytokines, and molecular signatures derived from tumor tissue [15,17]. Such biomarkers could eventually allow earlier detection of recurrence and reduce dependence on repeated imaging alone.

The cAMP/PKA pathway represents an attractive therapeutic target because it is central to PRKAR1A-related tumorigenesis. However, selective inhibition of this pathway remains challenging because PKA signaling is essential for normal physiological function in multiple organs.

Future strategies may involve targeted modulation of downstream pathways, including angiogenesis, inflammation, Wnt signaling, or epigenetic regulators. Although no pharmacological therapy currently replaces surgery, advances in molecular medicine may provide additional options for patients with recurrent, unresectable, or high-risk tumors.

CONCLUSIONS

Hereditary cardiac myxomas represent a clinically important subgroup of primary cardiac tumors in which genetic alterations play a central role in disease development. Carney complex, is the prototype disorder.

Compared with sporadic cardiac myxomas, hereditary tumors occur earlier, recur more frequently, and are associated with multisystem disease. Recognition of s appropriate genetic testing, and systematic family screening are therefore essential components of modern management.

Although surgery remains the cornerstone of treatment, continued research into genomic, epigenetic, and molecular mechanisms may lead to improved biomarkers and targeted therapies. A multidisciplinary approach integrating cardiology, cardiovascular surgery, endocrinology, pathology, and genetics remains essential for optimizing outcomes in affected patients.

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