

# Identification of a *PRKAR1A* mutation (c.491\_492delTG) in familial cardiac myxoma

## A case report

Shengjun Ma, MD<sup>a</sup>, Wei Liu, MD<sup>b</sup>, Anqi Zhang, PhD<sup>b</sup>, Li Pan, PhD<sup>b</sup>, Wenqiang Tang, MD<sup>b</sup>, Bo Jiang, MD<sup>b</sup>, Fengju Wang, MD<sup>b</sup>, Shuangfeng Chen, MD<sup>b</sup>, Bo Fu, PhD<sup>b,\*</sup>

### Abstract

**Rationale:** Cardiac myxoma is the most common cardiac neoplasm. Currently, there are not many reports on familial cardiac myxoma. Herein, we reported 2 first-degree relatives with left atrial myxoma.

**Patient concerns:** A 20-year-old female was admitted in our hospital for lapsing into a coma for 24 hours, and was diagnosed with recurrent left atrial cardiac myxoma. The patient's father also had a history of cardiac myxoma.

**Diagnosis:** The patient was diagnosed with left atrial myxoma using transthoracic echocardiography (TTE). Whole exome sequencing (WES) identified a p.Val164Aspfs (c.491-492delTG) mutation in the cAMP-dependent protein kinase A (PKA) regulatory (R) subunit 1 (*PRKAR1A*) gene for both the proband and her father, but not in her uncle and brother, who had not shown manifestation of cardiac myxoma by the time of this report.

**Interventions:** The myxoma resection was performed following the standard procedure of open chest surgery.

**Outcomes:** The tumor was successfully removed along with the tuberculum. The patient recovered well and was discharged home. No recurrence occurred during 1-year follow-up.

**Lessons:** Our findings suggest that *PRKAR1A* mutation (c.491\_492delTG) may be associated with cardiac myxoma, and genetic counseling and specific locus mutation tests may contribute to assessing the risk of cardiac myxoma.

**Abbreviations:** CNC = carney complex, CT = computed tomogram, ICU = intensive care unit, MRI = magnetic resonance images, PKA = cAMP-dependent protein kinase A, TTE = transthoracic echocardiogram, WES = whole exome sequencing.

**Keywords:** cardiac myxoma, diagnosis, *PRKAR1A* mutation, treatment

## 1. Introduction

Cardiac myxoma is the most common cardiac neoplasm that typically arises as an isolated mass in the left atrium.<sup>[1]</sup> In

approximately 3% to 10% cases, it occurs as one of the manifestations of the Carney complex (CNC).<sup>[2]</sup> Patients with cardiac myxoma in the context of CNC are prone to develop other syndromic manifestations and have higher rates of tumor occurrence, and cardiac myxoma has been found with familial tendency.<sup>[2]</sup> Imaging materials, including transthoracic echocardiogram (TTE), cardiac computed tomogram (CT) and cardiac magnetic resonance images (MRI), are pivotal in the diagnosis, management guidance, and surveillance of cardiac myxoma.<sup>[3]</sup> Surgical excision of the cardiac myxomas is the established definitive treatment and is highly efficacious.<sup>[4]</sup> Previous reports on molecular etiology of CNC have identified that mutation of the cAMP-dependent protein kinase A (PKA) regulatory (R) subunit 1 (*PRKAR1A*) gene was associated with CNC.<sup>[1,5]</sup>

Currently, there are not many reports on familial cardiac myxoma. In this article, we report 2 first-degree relatives who were diagnosed with left atrial myxoma and have undergone surgical resection. Whole exome sequencing (WES) was conducted to identify the mutated genes related to cardiac myxoma. This article illustrates the diagnosis and management of a case of familial atrial myxoma, and highlights the responsibility of pathogenic gene variants for familial cardiac myxoma.

### 1.1. Case presentation

**1.1.1. Ethical statement.** This study has been approved by the Ethics Committee of our hospital (ethical approval number: 2017096). Informed written consent was obtained from the patient for publication of this case report and accompanying images.

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This study has been approved by the Ethics Committee of our hospital (ethical approval number: 2017096). Informed written consent was obtained from the patient for publication of this case report and accompanying images.

The authors confirm that there are no conflicts of interest.

<sup>a</sup> Department of Cardiac Surgery, Liaocheng People's Hospital, Liaocheng, China, <sup>b</sup> Department of Central Laboratory, Liaocheng People's Hospital, Liaocheng, China.

\* Correspondence: Bo Fu, Department of Central Laboratory, Liaocheng People's Hospital, 67 Dongchang west Road, Liaocheng, Shandong 252000, China (e-mail: fubo.22@163.com).

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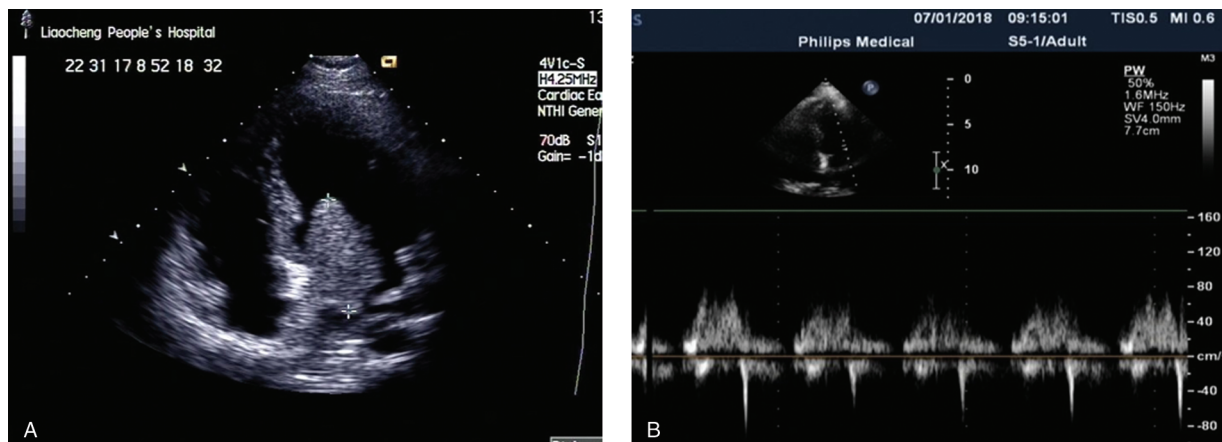


Figure 1. Left ventricular long axis view of transthoracic echocardiography (TTE) (A) before and (B) after the surgery.

### 1.2. Patient features and investigations

A 20-year-old female has a history of left atrial cardiac myxoma, which was diagnosed in 2015 and surgical resection was performed to remove the myxoma. In 2018, the patient was admitted in our hospital for lapsing into a coma for 1 day, and was diagnosed with recurrent left atrial cardiac myxoma (Fig. 1A). Physical examination did not reveal any yellow stain or bleeding spots on skin or mucous membrane of the whole body, and no thyroid nodule was found upon palpation. Diastolic murmur was present on cardiac auscultation; ultrasonography indicated the presence of an  $18 \times 18 \times 47$  mm mass at the left atrial septum.

### 1.3. Treatment

After routine examinations, myxoma resection was performed following the standard procedure of open chest surgery. Transverse aortotomy indicated the presence of a pedunculated myxoma mass of  $3 \times 2 \times 3$  cm at the left atrial septum. The tumor was successfully removed along with the tuberculum (Fig. 1B).

### 1.4. Outcome and follow up

After the surgery, the patient was transferred to the intensive care unit (ICU). The patient recovered well and was discharged home. No recurrence occurred during 1-year follow-up.

### 1.5. Family history

A family pedigree across 3 generations was constructed for the patient (Fig. 2). The proband's father (44 years old) was diagnosed with atrial cardiac myxoma and the mass has been surgically resected, therefore we speculated that the cardiac myxoma of the proband may be genetically related. The proband's uncle (38 years old) and brother (12 years old) did not show similar examination findings.

### 1.6. Whole exome sequencing (WES)

Peripheral blood specimens were collected for the patient, her father, uncle, and brother. Specimens of the patient's mother and grandparents were not able to be obtained. WES was performed to identify probable pathogenic variants responsible for familial cardiac myxoma. Bioinformatics analyses of WES identified a p. Val164Aspfs (c.491-492delTG) mutation in the *PRKARIA* gene for both the patient and her father, but not in her uncle and brother. The results were further confirmed by Sanger sequencing (Fig. 3).

## 2. Discussion

Myxomas are the most common primary cardiac tumor. It often occurs at 30 to 60 years old and the most common type is atrial myxoma. Mostly myxoma occurs without familiarity, but a few

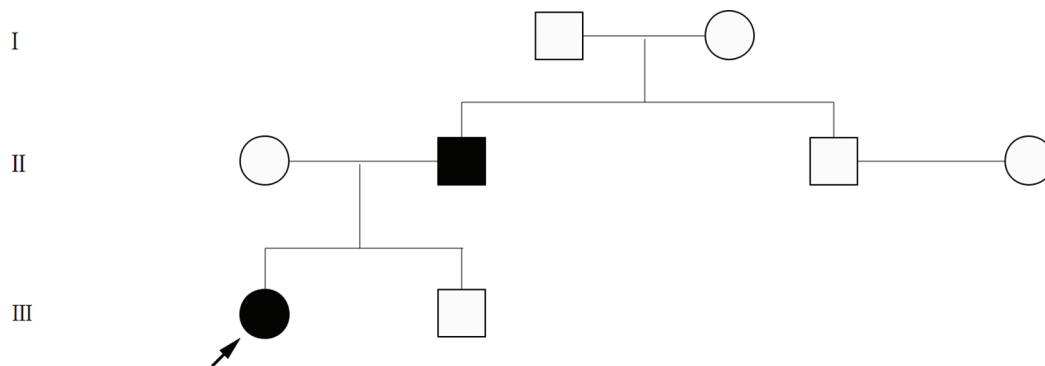
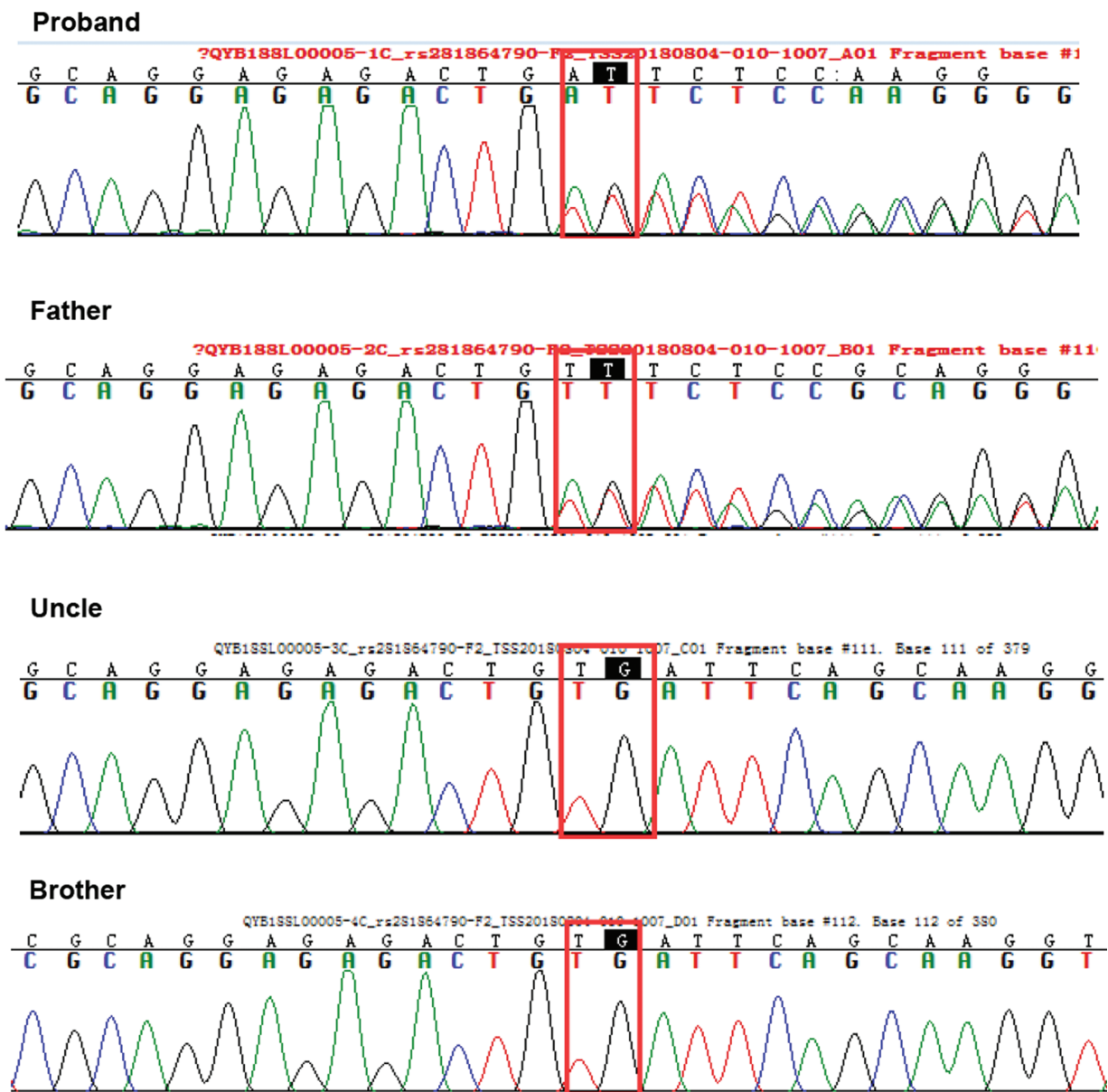


Figure 2. Pedigree of the family with cardiac myxoma. Arrow indicates the proband.



**Figure 3.** Gene mutation in the patients and his family. Both cardiac myxoma cases in the family (the proband and her father) carried the same *PRKAR1A* exon 5 mutation (c.491-492delTG), and her uncle and younger brother did not carry the mutation. *PRKAR1A*, protein kinase type I-alpha regulatory subunit.

cases showed a familial genetic tendency in a pattern of autosomal dominant inheritance. Recurrence of atrial myxomas is uncommon.<sup>[1,4]</sup> In this article, we reported 2 first-degree relatives with cardiac myxoma and the proband had recurrence 3 years after the first operation.

Mounting evidence indicated that loss of *PRKAR1A* expression may play a role in myxoma tumorigenesis. Studies on its molecular mechanism revealed that the regulatory subunit R1 binds to the catalytic subunits of protein kinase A, inactivating the holoenzyme *PRKAR1A*. Mutant-associated loss of *PRKAR1A* function may lead to increased cAMP-stimulated activity of protein kinase A, which may promote tumorigenesis.<sup>[6]</sup> More than 100 different mutations have been reported within the coding region of *PRKAR1A*.<sup>[7]</sup> Online *PRKAR1A* mutation database has been established by Horvath to facilitate the characterization of pathogenic variants.<sup>[8]</sup> *PRKAR1A* mutations

have been detected in two-thirds of CNS-associated cardiac myxoma.<sup>[9]</sup> *PRKAR1A* appears to play a role in the development of both syndromic and non-syndromic cardiac myxoma.<sup>[2]</sup>

We identified a putative causal gene variant of *PRKAR1A* that included the deletion of TG nucleotides at the position 491–492 in 2 first-degree relatives with cardiac myxoma (the proband and her father), but not in her uncle and brother, who did not show sign of cardiac myxoma. This mutation was included in the Clinvar database as a pathogenic mutation (<https://www.ncbi.nlm.nih.gov/clinvar/variation/12662/>). Consistently, Wang et al identified a c.491-492delTG mutation in *PRKAR1A* in a recurrent left atrial myxoma family.<sup>[10]</sup> The TG deletion is a frameshift mutation of *PRKAR1A*, which leads to the premature termination of polypeptide chain synthesis and increased cAMP-stimulated kinase activity, which may initialize tumorigenesis.<sup>[11]</sup>

Familial atrial myxoma is usually inherited as an autosomal dominant trait, which means *PRKAR1A* variation carriers inherit the mutation from their parents, and their siblings and offsprings have a 50% chance of carrying the same mutation. Therefore, it is recommended that the first- and second-degree relatives of patients undergo genetic counseling and specific locus mutation tests to assess the risk of myxomatosis. Appropriate genetic test may detect mutant carriers who have high risk of atrial myxoma and should be closely monitored by TTE, therefore set the stage for early detection and early application of effective therapy.

### 3. Conclusions

This article presents a familial case of 2 first-degree relatives with cardiac myxoma. The proband was diagnosed with recurrent left atrial myxoma and underwent surgical resection. WES analysis identified the c.491-492delTG mutation in *PRKAR1A* in the 2 patients (proband and her father), but not in her uncle and brother, who had not shown manifestation of cardiac myxoma as of this article drafting. Our findings suggest that *PRKAR1A* mutation (c.491\_492delTG) may be associated with cardiac myxoma, and genetic consulting and specific locus mutation tests may contribute to assessing the risk of cardiac myxoma.

### Author contributions

**Investigation:** Shengjun Ma, Wei Liu, Anqi Zhang, Li Pan, Wenqiang Tang, Bo Jiang, Fengju Wang, Bo Fu.

**Project administration:** Shengjun Ma.

**Supervision:** Shengjun Ma, Bo Fu.

**Validation:** Shuangfeng Chen.

**Writing – original draft:** Bo Fu.

**Writing – review & editing:** Wei Liu, Anqi Zhang.

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