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Basic Research

A Novel Inherited Mutation in *PRKAR1A* Abrogates PreRNA Splicing in a Carney Complex Family

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ABSTRACT

Background: Carney complex (CNC) is an autosomal dominant inherited disease, characterized by spotty skin pigmentation, cardiac and cutaneous myxomas, and endocrine overactivity. We report on a Chinese CNC family with a novel mutation in the protein kinase A regulatory subunit 1 (*PRKAR1A*) gene.

Methods: Target-exome sequencing was performed to identify the mutation of *PRKAR1A* in 2 members of the CNC family.

Results: The proband was a young man with typical CNC, including pigmentation, cutaneous myxomas, cardiac myxoma, Sertoli cell tumour of his left testis, and multiple hypoechoic thyroid nodules. His mother also had CNC with skin pigmentation, cutaneous myxomas, and a cardiac myxoma. Target-exome capture analysis revealed that the proband and the mother carried a novel heterozygous mutation in the exon 6 splicing donor site of *PRKAR1A*. Sequencing analysis of myxoma

RÉSUMÉ

Introduction : Le complexe de Carney (CNC) est une maladie héréditaire autosomique dominante, caractérisée par une pigmentation tachetée de la peau, des myxomes cardiaques et cutanés, et une hyperactivité endocrinienne. Nous rapportons un cas de CNC d'une famille chinoise avec une nouvelle mutation du gène de la sous-unité régulatrice 1 de la protéine kinase A (PRKAR1A).

Méthodes : Un séquençage ciblé de l'exome a été réalisé afin d'identifier la mutation de PRKAR1A chez 2 membres de la famille présentant un CNC.

Résultats : Le probant était un jeune homme avec un CNC caractéristique, incluant une pigmentation, des myxomes cutanés, un myxome cardiaque, une tumeur des cellules de Sertoli de son testicule gauche, et plusieurs nodules thyroïdiens hypoéchogènes. Sa mère avait également un CNC avec une pigmentation de la peau, des

Carney complex (CNC) is a rare autosomal dominant inherited disease characterized by spotty skin pigmentation, cardiac and cutaneous myxomas, and endocrine overactivity.[1-5] The syndrome was first described in 1985 by Carney et al.[6] Cardiac myxoma is the most common cause of death in CNC patients. The diagnostic criteria of the syndrome have recently been modified.[7]

Mutation of the cAMP-dependent protein kinase A (PKA) regulatory (R) subunit 1 (*PRKAR1A*) gene has been identified as a cause of CNC.[8] More than 1000 patients with CNC have been reported, of whom approximately 70% are familial cases. *PRKAR1A* mutation is found in >70% of CNC patients, and >100 different mutations have been reported throughout the coding region of *PRKAR1A*.[9,10] Horvath et al. reviewed all the known *PRKAR1A* mutations[10] and established an online database (http://PRKAR1A.nichd.nih.gov). However, little is known about the role of the *PRKAR1A* mutation in the development of CNC in Asian populations.

In this communication, we report on a Chinese CNC family characterized by cardiac and cutaneous myxomas, skin pigmentation, and multiple hypoechoic thyroid nodules. Using target-exome capture, we identified a novel mutation in the *PRKAR1A* gene in this family.

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messenger RNA revealed that the mutation abrogated exon 6 preRNA splicing, leading to a frameshift starting at Valine 185 and premature translation termination in intron 6. The truncated enzyme lacks the functional cyclic adenosine monophosphate (cAMP) binding domain at the C-terminus, causing PRKAR1A haploinsufficiency.

Conclusions: In this study we report on a novel splicing mutation in the *PRKAR1A* gene that adds to the genetic heterogeneity of CNC.

myxomes cutanés, et un myxome cardiaque. L'analyse de la capture de l'exome ciblé a révélé que le probant et la mère portaient une nouvelle mutation hétérozygote dans le site donneur d'épissage de l'exon 6 de PRKAR1A. L'analyse du séquençage de l'ARNm du myxome a révélé que la mutation a abrogé l'épissage du pré-ARN de l'exon 6, conduisant à un décalage du cadre de lecture à partir de la valine 185 et à une fin prématurée de la traduction dans l'intron 6. L'enzyme tronquée est dépourvue du domaine fonctionnel de fixation à l'AMPc au niveau C-terminal, provoquant une haploinsuffisance de PRKAR1A.

Conclusions : Dans cette étude, nous rapportons une nouvelle mutation d'épissage du gène PRKAR1A qui ajoute à l'hétérogénéité génétique de la CNC.

Methods

The protocol for this study was prospectively reviewed and approved by the Human Medical Ethical Review Committee at Jilin University First Hospital, and informed consent was obtained from each member of the family.

The proband

The patient was a 20-year-old man who was admitted to the hospital for removal of a right ventricular myxoma and a testicular tumour. A Sertoli cell tumour of his left testis had been surgically removed 10 years before admission. On physical examination, extensive pigmentation was observed on his face, especially on his upper lips (Supplemental Fig. S1A). Cutaneous myxomas (0.5 cm in diameter) were located on both ears (Supplemental Fig. S2). The right testis was enlarged. Echocardiography revealed an intracardiac tumour in the right ventricle affecting the tricuspid valve (Supplemental Fig. S3A). Thyroid ultrasonography was used to detect multiple small hypoechoic thyroid nodules, and the patient was euthyroid.

Although his growth hormone level was somewhat increased at 3.6 ng/mL, the patient did not have an acromegalic appearance. No sellar abnormalities were seen on a pituitary computed tomography scan. An abdominal computed tomography scan revealed a slightly enlarged left adrenal gland. Based on clinical manifestations and family history, the patient was diagnosed with CNC and the cardiac myxoma was removed. The myxoma originated in a papillary muscle and was adherent to the anterior tricuspid valve leaflet chordae (Supplemental Fig. S3B).

The mother with CNC

The mother was 48 years old. A left atrium myxoma located at the root of the posterior mitral valve leaflet had been resected 20 years previously. She suffered a cerebral infarction due to recurrent left atrium myxoma 2 years previously, and underwent another cardiac surgery to remove the mass 1 month after the stroke. She also had a history of recurrent cutaneous myxomas of her left nipple. She had multiple areas of pigmentation on her face (Supplemental Fig. S1B). Thyroid and pituitary function were normal. Thyroid ultrasonography was used to detect multiple small hypoechoic thyroid nodules.

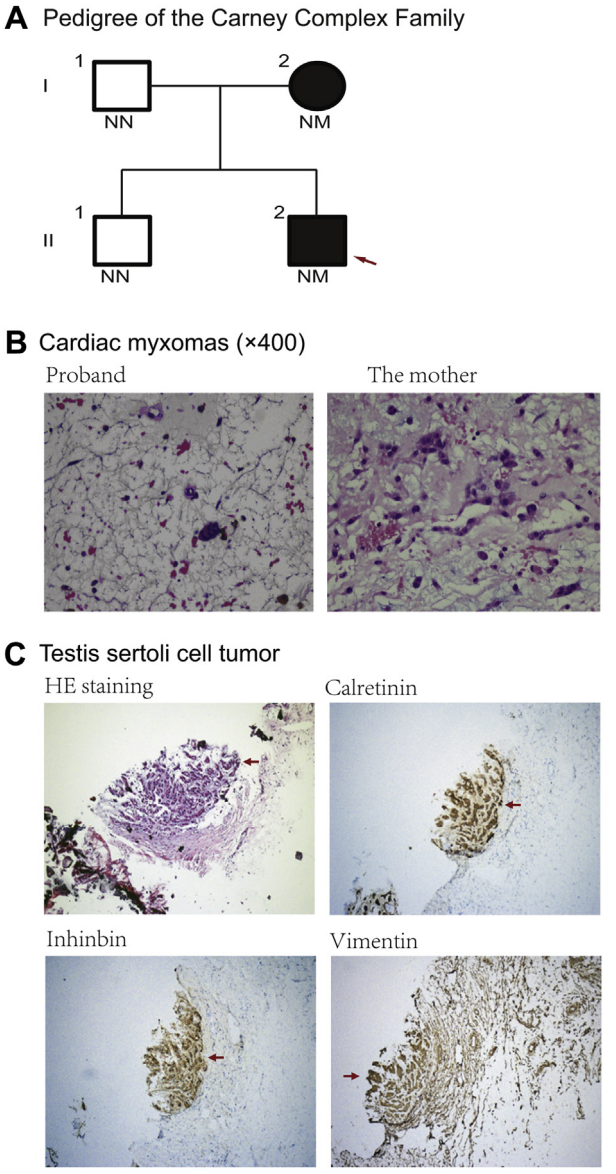

Figure 1. Pedigree of the Carney complex family. (**A**) The Carney complex pedigree. The proband is noted by an **arrow**. (**B**) Pathological findings of cardiac myxoma in the proband and the mother. Hematoxylin and eosin (HE) staining; magnification, 400×. (**C**) Pathological and immunohistochemical staining of Sertoli cell tumour from right testis aspiration biopsy. Magnification, 100×. NM, heterozygous mutation; NN, normal.