Two novel mutations of the *MYBPC3* gene identified in Chinese families with hypertrophic cardiomyopathy

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J Lin, D-D Zheng, Q Tao, et al. Two novel mutations of the *MYBPC3* gene identified in Chinese families with hypertrophic cardiomyopathy. *Can J Cardiol* 2010;26(10):518-522.

BACKGROUND: Hypertrophic cardiomyopathy (HCM) is one of the most common genetic cardiovascular disorders. Mutations in the *MYBPC3* gene are one of the most frequent genetic causes of HCM.

OBJECTIVES: To screen *MYBPC3* gene mutations in Chinese patients with HCM, and analyze the correlation between the genotype and the phenotype.

METHODS: The 35 exons of the *MYBPC3* gene were amplified by polymerase chain reaction in the 11 consecutive unrelated Chinese pedigrees. The sequences of the products were analyzed and the mutation sites were determined. The clinical data of genotype-positive families were collected, and the correlation between genotype and phenotype was analyzed.

RESULTS: Two mutations of the *MYBPC3* gene were confirmed among 11 pedigrees. A frameshift mutation (Pro459fs) was identified in exon 17 in family H8, and a splice mutation (IVS5+5G→C) was identified in intron 5 in family H3. These two mutations were first identified in Chinese patients with familial HCM and were absent in 110 chromosomes of healthy controls. Seven known polymorphisms were found in the cohort.

CONCLUSIONS: Compared with what was reported abroad, the *MYBPC3* gene is a common pathogenic gene responsible for HCM in Chinese patients, and the phenotypes of these two mutations in their respective families may have their own clinical characteristics.

Key Words: Familial hypertrophic cardiomyopathy; Genotype; Mutation; *MYBPC3*; Phenotype

Hypertrophic cardiomyopathy (HCM) is one of the most common cardiovascular disorders characterized by idiopathic hypertrophy of the left or right ventricle in the absence of loading conditions sufficient to cause myocardial hypertrophy, such as congenital heart disease, obstructive valvular heart disease, hypertension and metabolic diseases (1). Estimates of the prevalence of the HCM phenotype within the general American and Chinese population are very close at approximately 0.2% and 0.18%, respectively (2,3).

Over the past 20 years, HCM has been defined as a disease of the cardiac sarcomere that is generally transmitted as a Mendelian trait with an autosomal-dominant pattern of inheritance (4). At least 50% of familial HCM and 20% to 30% of sporadic HCM result from mutations in the known causative genes (5). To date, more than 450 various mutations in at least 13 genes responsible for HCM have been identified, most of which encode cardiac sarcomeric contractile or regulatory proteins (6). According to previous studies, one of the most predominant mutant genes is the *MYBPC3* gene, which accounts for approximately 20% to 25% of genotyped cases of HCM (7). *MYBPC3* maps to chromosome 11p11.2 locus, comprises over 21 kb and contains 35 exons, of which 34 encode 1274 amino

Deux nouvelles mutations du gène *MYBPC3* repérées dans des familles chinoises présentant une myocardiopathie hypertrophique

HISTORIQUE : La myocardiopathie hypertrophique (MCH) est l'un des troubles cardiovasculaires génétiques les plus courants. Les mutations du gène *MYBPC3* font partie des causes génétiques les plus fréquentes de MCH.

OBJECTIFS : Dépister les mutations du gène *MYBPC3* chez les patients chinois atteints de MCH et analyser la corrélation entre le génotype et le phénotype.

MÉTHODOLOGIE : Les chercheurs ont amplifié les 35 exons du gène *MYBPC3* par réaction en chaîne de la polymérase dans les 11 généalogies chinoises consécutives non liées. Ils ont analysé les séquences des produits et déterminé les foyers de mutation. Ils ont colligé les données cliniques des familles positives au génotype et analysé la corrélation entre le génotype et le phénotype.

RESULTATS : Les chercheurs ont confirmé deux mutations du gène *MYBPC3* dans 11 généalogies. Ils ont repéré un déphasage du cadre de lecture (Pro459fs) à l'exon 17 de la famille H8, ainsi que la mutation d'un site d'épissage (IVS5+5G→C) dans l'intron 5 de la famille H3. Ces deux mutations ont d'abord été repérées chez des patients chinois ayant une MCH familiale et étaient absentes dans 110 chromosomes de sujets témoins en santé. Ils ont trouvé sept polymorphismes connus dans la cohorte.

CONCLUSIONS : Par rapport à ce qui a été déclaré à l'étranger, le gène *MYBPC3* est un gène pathogène courant responsable de la MCH chez les patients chinois, et les phénotypes de ces deux mutations dans leur famille respective peuvent avoir leurs propres caractéristiques cliniques.

acids (8). In other genes causing HCM, the majority of gene variants are missense mutations, resulting in a single amino acid residue substituted. By contrast, 70% of all mutation types in *MYBPC3* are nonsense mutations including frameshift, insertion/deletion and splice site mutations (9).

For the purpose of screening the spectrum of *MYBPC3* mutations in Chinese patients afflicted with HCM and analyzing the correlation between the genotype and the phenotype, we investigated 11 consecutive unrelated Chinese families affected by HCM using the polymerase chain reaction (PCR) method.

METHODS

Subjects

Eleven index patients from different pedigrees, diagnosed at the First Affiliated Hospital of Soochow University (Suzhou, China), with unequivocal familial HCM between 2002 and 2008 were recruited. The control group consisted of 110 unrelated healthy individuals.

The study protocol was approved by the Ethics Committee on Medical Research of the First Affiliated Hospital of Soochow University

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Received for publication November 9, 2009. Accepted April 28, 2010

TABLE 1
Putative hypertrophic cardiomyopathy-causing mutations and polymorphisms identified in MYBPC3

Exon (E) or intron (I)	Nucleotide change*	Amino acid change	Mutation type
E17	del C	Pro459fs	Frameshift mutation
I5	GTGAG→GTGAC	IVS5+5G→C	Splice mutation
I3	G→C	—	Polymorphism
I13	C→T	—	Polymorphism
I24	C→G	—	Polymorphism
I5	ins C	—	Polymorphism
E7	AGC→GGC	Ser236Gly	Polymorphism
E26	GTC→GTT	Val894Val	Polymorphism
E31	GAA→GAG	Glu1096Glu	Polymorphism

*GenBank (National Institutes of Health, USA) accession number U91629. del Deletion; ins Insertion

and conformed to the principles of the Declaration of Helsinki. All subjects gave informed consent of their own free will.

Clinical evaluation

The clinical investigation included presenting symptoms, clinical history, physical examination, 12-lead electrocardiography (ECG), and two-dimensional and Doppler echocardiography. All the clinical data of the probands and available relatives were collected before the genotypes were sequenced.

The major clinical diagnostic criteria of HCM was a maximal left ventricular wall thickness of at least 15 mm on two-dimensional echocardiography in the absence of other cardiac or systemic causes of ventricular hypertrophy. Left ventricular outflow tract obstruction (LVOTO) was measured as a peak instantaneous gradient of at least 30 mmHg in the resting state (10,11). ECG abnormalities were defined as pathological Q waves, giant T wave inversions or unexplained left ventricular hypertrophy. Relatives who had both the affected gene (which was identified in the subsequent genetic analysis) and borderline hypertrophy (wall thickness of 11 mm to 14 mm) or abnormal ECG were considered to be affected with HCM (11,12). Sudden death was defined as unexpected death occurring within 1 h after the onset of symptoms that were not apparent or diagnosed clinically before. Deceased members were considered to have been affected when a diagnosis of HCM had been documented in the clinical records that could be supported by family history or their offspring's genotypes.

DNA analysis

In previous reports (13-15), the present cohort had been searched for variants in three HCM-causing genes encoding for beta-myosin heavy chain (MYH7), cardiac troponin T (TNNT2) and troponin I (TNNI3). Because no disease-causing mutations had been identified in the aforementioned genes, MYBPC3 was chosen to be the candidate gene in the present study.

Peripheral blood specimens were taken from all subjects, and genomic DNA was isolated from leukocytes using a QIAGEN DNA purification kit (QIAGEN GmbH, Germany) in compliance with the protocols of the manufacturer. The primers were designed according to the published articles. All 35 coding exons with their flanking intronic sequences of MYBPC3 were amplified with PCR performed on an ABI 2400 Thermal Cycler (Applied Biosystems, USA), and then the products were directly analyzed on an ABI Prism 3730XL automated sequencing system (Applied Biosystems) by dideoxy chain termination reaction.

RNA analysis

If an intronic mutation was found, the carrier was recalled and asked to provide a second blood specimen. Total RNA was extracted from the second blood specimen using Trizol reagent (Invitrogen, USA) and

Figure 1 Pedigrees of two families carrying the mutations Pro459fs (family H8) and IVS5+5G→C (family H3). Symbols denote gender and disease status: box = male; circle = female; darkened = full phenotype of hypertrophic cardiomyopathy; clear = unaffected; slashed = deceased; ? = uncertain

reverse transcribed into complementary DNA using RevertAid First Strand cDNA Synthesis Kit (MBI Fermentas, Lithuania) according to the manufacturer's protocol. Reverse transcription-PCR amplification products were subcloned into the pMD18-T vector by using the TA Cloning Kit (Invitrogen) and were sequenced for confirmation of identity as described above. The concrete steps of PCR were as represented previously (13,14), and the sequences of primers are available on request.

All results of the sequence analysis were aligned with the standard sequence of MYBPC3 supplied by GenBank (National Institutes of Health, USA) using Sequencer software (Gene Codes, USA). If the abnormal gene fragment was detected in the proband, the relevant exon or intron of all the relatives in this pedigree was bidirectionally sequenced. Moreover, 110 chromosomes of healthy controls were screened to ascertain whether the new variant was a pathogenic mutation or a gene polymorphism.

RESULTS

Genetic results

To determine the spectrum of MYBPC3 mutations, the coding exons and flanking sequences of MYBPC3 in the 11 consecutive unrelated Chinese families involved in familial HCM were scanned. Nine different gene variants, including seven polymorphisms and two novel mutations, were found (Table 1). All of the polymorphisms screened in MYBPC3 were identified in control individuals and recorded in the Single Nucleotide Polymorphism database of the United States National Center for Biotechnology Information (NCBI). The two mutations (Pro459fs and IVS5+5G→C) were sequenced in two pedigrees (H8 and H3, respectively) and were found to be absent in 110 healthy chromosomes (Figure 1).

A frameshift mutation (Figure 2), Pro459fs, deleting one nucleotide (cytosine) at base position 10739 in exon 17, was found in the proband (III-2) of family H8, which led to a reading frameshift after code 459, resulting in a premature termination codon (TGA) at code 465 in one of the alleles of MYBPC3. This eventually produced an abnormal transcript. This mutation was counted as cosegregated with HCM phenotype in family H8, based on the fact that it was present in the index patient's mother (II-1) diagnosed with HCM and absent in other healthy close relatives.

In family H3, a heterozygous mutation (GTGAG→GTGAC substitution) (Figures 3A and 3B) was detected 5 bp downstream of the 5' splice donor in intron 5 of MYBPC3. In other words, cytosine was replaced by guanosine at base position 3672 in the DNA sequence. The IVS5+5G→C mutation was expected to disrupt the consensus splice donor site of intron 5, whereas both amplification and subcloning of the aberrant complementary DNA fragment confirmed the activation of a cryptic donor splicing site positioned upstream, and

Figure 2) Sequencing analysis of exon 17. **A** Normal portion of the sequence of the polymerase chain reaction-amplified exon 17 fragment. **B** The same fragment from an affected member containing the cytosine deletion in position 10739 (arrow)

identified the deletion of 10 nucleotides (GTGACCGTGG) of exon 5 (Figures 3C and 3D). Therefore, this change introduced a frameshift after the amino acid glutamic acid at code 165 that synthesized a truncated protein incorporating 15 aberrant amino acids, followed by a premature termination codon (TGA) at code 184. Both the proband (III-2) and his father (II-1) carried the same splice site mutation, and the genotypes of other available unaffected family members were normal. This result showed a cosegregation of the mutation with the disease in family H3.

Clinical features

Through careful auxiliary examinations, the clinical characteristics of all available family members in these two pedigrees were systemically evaluated (Table 2).

The proband (III-2) of family H8, who was diagnosed with HCM on routine medical examination at 24 years of age, was a female patient without clinical symptoms. The echocardiographic examination at that time indicated that posterior wall thickness and ejection fraction were normal (9 mm and 77%, respectively), and the marked thickness of the interventricular septum was 28 mm. At the 10-year follow-up, serial echocardiographic images had almost the same findings. On ECG, the proband had a slight ST segment depression in the inferior leads, and flattened or negative T waves in the right precordial leads. Her 61-year-old mother (II-1), who carried the identical

Figure 3) Sequencing analysis of intron 5. **A** Normal portion of the sequence of the polymerase chain reaction-amplified intron 5 fragment. **B** The same fragment from an affected member containing the G→C transversion in position 542 (arrow). **C** Normal portion of the TA clone sequencing of reverse transcription-polymerase chain reaction product fragment. **D** The same fragment from an affected member containing the deletion of GTGACCGTGG (box in C)

mutation, diagnosed in the course of family screening for HCM two years previously, was asymptomatic. ECG showed that pathological Q waves were present in the inferior leads, and the last echocardiographic re-examination showed no significant changes compared with the initial recording, which revealed that the thickness of the interventricular septum was 20 mm. All other family members had normal ECG and echocardiographic results.

In family H3, the index patient (III-2) and his father (II-1) had apparent asymmetrical septal hypertrophy (33 mm and 22 mm, respectively) and LVOTO in the resting state. The proband, a 46-year-old man, who was diagnosed at 40 years of age with occasional dyspnea and palpitations, received long-term treatment with a beta-adrenergic blocking drug. During the six-year period of follow-up, posterior wall

TABLE 2
Clinical characteristics of all the mutation carriers from the two families

Family	Subjects	Sex	Age, years			ECG		Echocardiogram at diagnosis/study					
			At study	At diagnosis	Symptoms	ST	Q	IVS, mm	PW, mm	LVDD, mm	LVEF, %	LAD, mm	LVOTO
H8	II-1	Female	61	59	None	+	+	20/18	7/11	40/40	78/79	36/28	–
	III-2	Female	34	24	None	+	–	28/28	9/8	40/40	77/77	30/34	–
H3	II-1	Male	73	73	None	+	–	–/22	–/15	–/36	–/69	–/44	+
	III-2	Male	46	40	Dyspnea, palpitations	+	–	33/33	12/19	41/44	69/85	38/35	+

+ Present; – Absent; ECG Electrocardiogram; IVS Interventricular septal thickness; LAD Left atrium dimension; LVDD Left ventricle diastolic dimension; LVEF Left ventricular ejection fraction; LVOTO Left ventricular outflow tract obstruction; PW Posterior wall thickness; Q Abnormal Q wave; ST ST-T wave abnormalities

TABLE 3
Conservation of the mutated MYBPC3 residue among various species

Pro495fs	459*																			
Subject	V	L	I	T	R	P	W	R	T	S	W	TER	–	–	–	–	–	–	–	
Human	V	L	I	T	R	P	L	E	D	Q	L	V	M	V	G	Q	R	V	E	F
Mouse	V	L	I	T	R	S	L	E	D	Q	L	V	M	V	G	Q	R	V	E	F
Rat	V	L	I	T	R	S	L	E	D	Q	L	V	M	V	G	Q	R	V	E	F
Chicken	I	L	I	T	H	P	L	E	D	Q	M	V	M	V	G	E	R	V	E	F
<i>Bos taurus</i>	V	L	I	T	R	P	L	E	D	Q	L	V	M	V	G	Q	R	V	E	F
<i>Canis lupus</i>	V	L	I	T	R	P	L	E	D	Q	L	V	M	V	G	Q	R	V	E	F
<i>Gallus gallus</i>	I	L	I	T	H	P	L	E	D	Q	M	V	M	V	G	E	R	V	E	F
<i>Danio rerio</i>	V	L	I	V	R	N	L	E	D	Q	M	A	M	K	G	D	R	V	E	F
<i>Xenopus tropicalis</i>	V	Q	I	L	H	S	L	E	D	Q	M	V	M	V	G	E	R	V	E	F
IVS5+5G→C	165*																			
Subject	E	–	–	–	V	A	A	S	P	S	Q	P	A	W	P	A	P	A	S	TER
Human	E	V	T	V	G	G	S	I	T	F	S	A	R	V	A	G	A	S	L	L
Mouse	E	V	T	V	G	G	S	I	V	F	S	A	R	V	A	G	A	S	L	L
Rat	E	V	T	V	G	G	S	I	V	F	S	A	R	V	A	G	A	S	L	L
Chicken	E	V	T	V	G	G	N	I	T	F	T	A	K	V	A	G	E	S	L	L
<i>Bos taurus</i>	E	V	T	V	G	G	T	I	T	F	S	A	R	V	A	G	A	S	L	L
<i>Canis lupus</i>	E	V	T	A	G	G	S	I	T	F	S	A	R	V	A	G	A	S	L	L
<i>Gallus gallus</i>	E	V	T	V	G	G	N	I	T	F	T	A	K	V	A	G	E	S	L	L
<i>Danio rerio</i>	E	V	N	V	G	E	N	I	I	F	I	A	R	V	C	G	E	S	L	L
<i>Xenopus tropicalis</i>	E	I	T	V	G	S	N	I	K	F	T	A	R	I	A	G	A	N	L	I

*The number shows the site of mutation. TER Termination codon

thickness and left ventricular outflow tract gradient were significantly elevated: from 12 mm to 19 mm, and from 28 mmHg to 88 mmHg, respectively. His father, who was 73 years of age, had no symptoms with a mild left atrial enlargement of 44 mm and a severe left ventricular outflow tract pressure gradient of 86 mmHg measured by echocardiography. The index patient's brother (III-1) succumbed to sudden cardiac death (SCD) at 20 years of age. In other available relatives, no phenotypic abnormalities were seen.

DISCUSSION

HCM is a primary genetic disease of the sarcomeric apparatus affecting the left or right ventricle, and often involves the ventricular septum (16). The clinical manifestation of HCM is multiform, ranging from asymptomatic to severe symptoms such as dyspnea, angina, syncope and heart failure. Furthermore, SCD, which is the most devastating complaint associated with HCM, often presents as an initial symptom, especially in young people (17). Nevertheless, noninvasive tests, such as ECG and echocardiography, could not be used to make the diagnosis until ventricular myocardium had morphological changes. Genetic testing, therefore, becomes an accurate and effective diagnostic method in the family affected with HCM.

Cardiac myosin-binding protein C belongs to the intracellular immunoglobulin superfamily and comprises 11 globular domains (C0 to C10) – including eight class I immunoglobulin motifs and three fibronectin type III motifs – of which C1 to C2 and C8 to C10 domains contain three phosphorylation sites, and the binding sites for myosin and titin, respectively (18). Thus, cardiac myosin-binding protein C is considered to be either a structural protein or a modulating protein in the myocardial sarcomere (19). In fact, in excess of 160 mutations have been reported so far in the MYBPC3 gene (6), and the majority of them are nonsense mutations that encode a C-terminally truncated protein with loss of the C8 to C10 domains (8).

In the present study, we identified nine variants of MYBPC3 in the 11 consecutive unrelated Chinese families afflicted with HCM. Seven of the nine variants were confirmed as single-nucleotide polymorphisms. The remaining two (Pro459fs and IVS5+5G→C), which were first found in familial HCM patients, could not be searched for

in the SNP database and were not detected in the chromosomes of 110 healthy adults. Furthermore, these two new variants affected the highly conserved region of the amino acid residue among various species (Table 3), and gave rise to truncated proteins with loss of the binding sites for myosin and titin, which disrupt the correct assembly of sarcomeres. In addition, in families H8 and H3, all the phenotype-positive individuals carried the corresponding variant and all the genotype-negative individuals had no clinical manifestation of HCM; thus these two variants in MYBPC3 cosegregated with HCM in their respective pedigrees. Consequently, Pro459fs and IVS5+5G→C were considered to be de novo pathogenic mutations instead of single-nucleotide polymorphisms.

Previous research (20-22) demonstrated that the clinical features of mutations in MYBPC3 are characterized by a mild degree of myocardial hypertrophy, a late-onset, relatively benign course and a longer life expectancy than for mutations in MYH7. Nonetheless, HCM is considered to be a disease of heterogeneity. The various clinical expressions of HCM result from different mutations or even identical genotype among diverse families. It likely illustrates that other factors, such as ethnic background, modifier genes and lifestyle, also play a role in the pathogenesis of HCM (6).

The Pro459fs mutation found in family H8 was predicted to cause an alteration in the open reading frame of the entire downstream sequence, generate a premature termination codon and then result in truncation of the protein lacking the myosin and titin-binding domains. Two genotype-positive individuals of the family with mild hypertrophy were asymptomatic, and the disease was inclined to progress slowly with a long-term follow-up – the longest being 10 years. All of these findings are in accordance with the clinical features of MYBPC3 as described above, while the frameshift mutation in this Chinese pedigree has its own character: two patients had undiagnosed HCM until they attended the medical examination because they had no clinical symptoms and, therefore, we considered that the age of onset of HCM (24 years) in this family seemed to be earlier than previously reported (21,23). In exon 17, two other nonsense mutations were found, which are close to Pro459fs and also resulted in a premature termination codon. Waldmüller et al (24) described the Pro453fs mutation in two Indian families that were

distantly related by a common founder. The clinical phenotypes of these two families are highly heterogeneous: one family has a benign course, whereas the other one has four cases of SCD. Recent literature (25) reported an Asp463stop mutation in a Chinese man who was diagnosed by medical examination with sporadic HCM. The clinical courses of this patient are somewhat similar to the phenotype of family H8: the early-onset of disease and moderate hypertrophy of interventricular septum.

Jääskeläinen et al (26) identified that a splice acceptor mutation (IVS5-2A→C) in a Finnish cohort with familial HCM was associated with the high penetrance and a relatively benign course characterized by mild clinical symptoms and moderate left ventricular hypertrophy. In the present study, we also observed a novel splice site mutation in the same intron (IVS5+5G→C), which was confirmed to activate a cryptic donor splicing site and produce an aberrant messenger RNA with the deletion of 10 nucleotides, thus affecting three putative phosphorylation sites between the C1 and C2 domains (8). The proband's brother (III-1) in family H3 suffered from SCD at 20 years of age. Although his blood sample was not collected, we supposed that this patient could also be a mutation carrier because SCD often occurs in young people with HCM, and because of the genotype of the proband and his father. Notwithstanding that the available family members with HCM were without arrhythmia events and severe symptoms, they also have two major risk factors of SCD, including a family

history of HCM-related premature SCD in one close relative and the thickness of interventricular septum greater than 30 mm, which is related to a long-term risk of SCD (11,27). Meanwhile, left ventricular outflow tract pressure gradient in family H3 (greater than 50 mmHg) is also considered to be a minor risk factor of SCD in HCM (11). In addition, despite treatment with a beta-adrenergic blocking drug, the proband showed significant change in the degree of myocardial hypertrophy and LVOTO during the six-year follow-up period. Accordingly, we presumed that the clinical course of HCM in family H3 could be malignant.

CONCLUSION

We reported two de novo pathogenic mutations (Pro459fs and IVS5+5G→C) in two Chinese pedigrees with familial HCM that were followed up for long-term periods of six years and 10 years, respectively. By analyzing the correlation between the genotype and the phenotype, the results of the study demonstrate the following: MYBPC3 is a common pathogenic gene of great importance that is responsible for HCM in Chinese patients; due to ethnic background variation, modifier gene effects and lifestyle, the clinical manifestations of these two MYBPC3 gene mutations presented their own clinical characteristics in contrast with the results of the former studies; and it is of practical significance to perform genetic testing on Chinese individuals with asymptomatic or mild symptoms.

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