Original Article

Epidemiology of Cardiomyopathy - A Clinical and Genetic Study of Hypertrophic Cardiomyopathy: The EPOCH-H study

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Abstract

Background: Hypertrophic cardiomyopathy (HCM) is a genetic disorder with the prevalence of 1 in 500 globally. HCM is clinically characterized by thickening of the wall of the heart, predominantly left ventricle (LV), and interventricular septum (IVS). Our study aims to report the demographical, clinical and genetic profile of Indian HCM patients. **Methods:** HCM patients were recruited on the basis of WHO criteria. The clinical phenotypes were analyzed using electrocardiography, two-dimensional electrocardiography, and hotspot region of the MYH7 gene was sequenced for all patients as well as for controls. **Results:** There were 59 patients with a clinical diagnosis of HCM with a preponderance of disease in males with a ratio (men, women) of 5.5:1. Average age of onset of the disease was late 30 s (39.2 ± 14.5) with familial HCM accounting for 18% (n = 9) for total HCM families (n = 50). Nonobstructive kind of HCM was more prevalent as compared to obstructive HCM (66.1% vs. 33.9%). Average posterior wall LV thickness of the HCM patients was 16 ± 4.8 mm and IVS thickness was 21 ± 8.3 mm with familial patients having greater wall thickness as compared to sporadic patients. Sequencing of hotspot region of MYH7 identified three mutations in three different patients. Two mutations were found to be segregating in familial cases. **Conclusion:** HCM is more prevalent in males with a predominance of hypertrophic nonobstructive cardiomyopathy form. Eighteen percent of cases were familial and showed an early onset of the disease and worse prognosis as compared to sporadic cases. Hotspot sequencing of MYH7 only explains 6% of its genetic basis. More of the candidate genes need to be screened through advanced techniques like next generation sequencing to identify the causal genes which could make us understand the mechanistic pathways.

Key words: Familial, genetics, hypertrophic cardiomyopathy, sporadic

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common autosomal dominant form of inherited primary myocardial disorder, characterized by hypertrophy or thickening of the left (sometimes right) ventricles with histological features of myocyte hypertrophy, myofibrillar disarray, and interstitial fibrosis. The estimated prevalence rate is 1 out of 500 young adults (<35 years of age).[1,2] The first clinical description of HCM was given in 1958 by Teare, who reported the sudden death in young patients.[3] The HCM is subdivided into two categories – obstructive and nonobstructive. The obstruction of the left ventricular outflow tract due to hypertrophy is defined as hypertrophic obstructive cardiomyopathy (HOCM) and no obstruction in the left ventricle (LV) outflow tract is hypertrophic nonobstructive cardiomyopathy (HNCM).[4,5]

The disease exhibits extreme variability, in terms of age of onset, disease progression, occurrence of sudden cardiac death (SCD), spectrum and extent of symptoms, and most noticeably, the degree, and location of hypertrophy.[6-9] Moreover, the disease heterogeneity can range from clinically and morphologically unaffected with an asymptomatic course and normal longevity, to severe dysfunction, including heart failure (HF), or SCD with the latter often being the first manifestation of the disease.[10-12] The first gene for familial HCM (FHCM) was mapped to chromosome 14q1.[13] In the past two decades, many causative mutations have been identified in sarcomeric and nonsarcomeric genes fostering the view that HCM is a complex disorder involving sarcomeric proteins and nonsarcomeric proteins. More than 25 genes are known to

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cause HCM till date, and around 1500 mutations are reported to be associated with HCM.[14]

The assessment of all the factors for the complete understanding is necessary for such complex disease. We hypothesized that unbiased representation of the spectrum of disease expression in HCM would require holistic assessment of HCM patients in the genetically heterogeneous population.

Methods

From our cohort of cardiomyopathy patients, we present HCM patients in the epidemiology of cardiomyopathy study-HCM study (EPOCH-H) in the second phase after dilated cardiomyopathy in the previous issue.[15] This cohort comprised HCM patients attending the HF clinic who fulfilled the following criteria: (1) Age ≥12 years; (2) referral with symptomatic HF with no hypertension or other cardiac causes which can cause hypertrophy of the LV or having proven HCM in the family, and/or features suggestive of HCM on prior investigations; and (3) clinical diagnosis of HCM in accordance with either task force guidelines[16] or modified diagnostic criteria for FHCM,[17] on the basis of standard noninvasive evaluation. Family members were invited to undergo genetic analysis and clinical investigation. The work follow-up included family history of HCM or any other disease, symptom assessment of patients, demographic details, clinical evaluation at the point of recruitment, 12-lead electrocardiography (ECG) and two-dimensional echocardiography for all the patients and family members who participated in the study. Ethical approval was taken from authorizing committees of both institutions. Workflow of the experiment is given in Figure 1.

Five milliliter of intravenous blood sample was collected with a prior written consent of all the participants who took part in this study. Genomic DNA was extracted using phenol-chloroform method,[18] for genetic testing. Primer sequences were designed and available on request. We sequenced hotspot region (exon 23) of MYH7 gene for variant identification using Sanger method (ABI3730XL) of all the patients and independently confirmed in DNA samples by repeated sequencing of independent polymerase chain reaction products. If any variant was identified in a proband, then family members were also screened for potential risk in family members. One hundred clinically evaluated controls were also screened for the variant identified. Statistical calculations were performed using online statistical calculators at http://departments.vassar.edu/lowry/VassarStats.html and SPSS Inc. Released 2009. PASW Statistics for Windows, version 18.0. SPSS Inc., Chicago.

Results

Basic characterization of the cohort

Out of 66 patients, 59 patients met the inclusion criteria for HCM and were included in the study and 7 patients did not participate in the study. Out of 59 patients, with the clinical diagnosis of the HCM, 50 (84.7%) were males and 9 (15.3%) were females. The demographic details are described in Table 1. The cohort included 50 families in which 9 families were having ≥2 affected individuals. FHCM accounted for 18% ($n = 9$) of total HCM families ($n = 50$), whereas sporadic cases were comparatively high. Average age of onset of disease

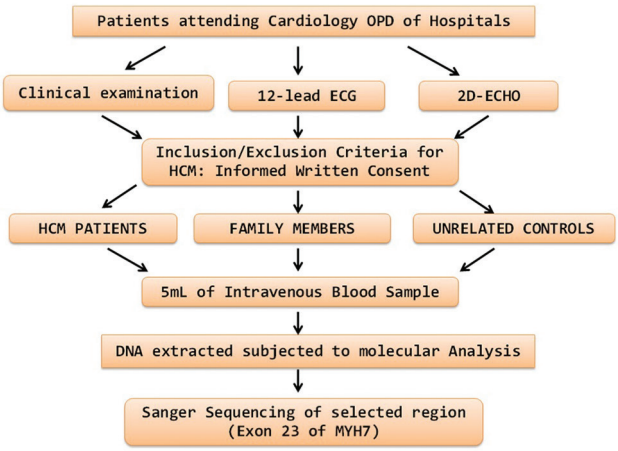

Figure 1: Workflow of the present study.

Table 1: Baseline characteristics of the study population

Variables	Total (%)	Familial (%)	Sporadic (%)	*P*
Number of HCM patients, *n*	59 (100)	18 (30.5)	41 (69.5)	<0.01
Number of families, *n*	50 (100)	9 (18)	41 (82)	<0.01
Age, year (mean±SD)	43.8±15.3	40.5±17.0	45.3±13.2	NS
Age at onset (mean±SD)	39.2±14.5	33.8±15.8	40.6±12.7	NS
Male, age at onset (mean±SD)	38.7±13.6	33.1±16.2	41.2±11.8	0.06
Female, age at onset (mean±SD)	37.4±16.7	37.6±15.8	37.2±19.1	NS
Sex ratio (men, women)	5.5:1 (50, 9)	5:1 (15, 3)	5.8:1 (35, 6)	NA
NYHA classes				
I	6 (12)	5 (27.8)	1 (2.4)	NS
II	38 (76)	8 (44.4)	30 (73.2)	
III	14 (28)	4 (22.2)	10 (24.4)	
IV	1 (2)	1 (5.6)	0 (0.0)	

P value calculated for familial versus sporadic; *Z*-test for a number of patients and families; *t*-test for age, age of onset (male and female); Chi-square for NYHA class. NS: Not significant, HCM: Hypertrophic cardiomyopathy, SD: Standard deviation, NYHA: New York Heart Association, NA: Not available

was late 30 s (39.2 ± 14.5) although out of the 59 patients, 7 patients had early age of onset (<20 years) and 5 out of 7 had familial form of HCM and other had sporadic HCM. The mean age of onset of symptoms in males was 38.7 ± 13.6 and 37.4 ± 16.7 in females. Familial cases had early onset of disease as compared to sporadic (familial [33.8 ± 15.8] vs. sporadic [40.6 ± 12.7]) although the difference was of borderline significance ($P = 0.06$). Males also had early onset of symptoms (33.1 ± 16.2) than females (37.6 ± 15.8) in familial cases [Table 1]. A total of 124 family members were also clinically evaluated for the HCM and recruited in this study. New York Heart Association (NYHA) class was similar in familial and sporadic cases.

Clinical characterization

Fifty-nine diagnosed individuals basically fell under two major categories - HOCM and HNCM. With 39 (66.1%) HNCM and 20 (33.9%) HOCM, they had a ratio of 2:1. Symptoms and signs of right-sided HF were not detected. Twelve (21.4%) patients reported to have syncopal episodes, and 4 (7.1%) had presyncope and other characteristics are detailed in Table 2. Most common form of the symptoms present in HCM cohort were chest pain (64.3%), shortness of breath (62.5%), and palpitation (53.5%). In the nonobstructive type of HCM, asymmetrical form of HCM was higher than other forms of HCM. Out of 59 patients, 2 (3.4%) HCM patients died suddenly, but a clinical autopsy was not conducted to confirm the cause of death. Thirteen (22.1) patients underwent alcohol ablation or trans-septal myectomy or had an implantable cardioverter defibrillator implant. Results are summarized in Figure 2.

Electrocardiography and echocardiographic evidences

ECG was available for all the 59 patients. ECG abnormalities were found in all HCM patients. ST-T abnormalities (93.2%) and pathological Q waves (93.2%) were there in patients. Both QRS duration ≥100 ms and bundle branch block were present in 27.1% of HCM patients. Giant T waves were seen mostly in the apical HCM patients. All familial cases attributed to ST-T abnormalities and most of the patients (83.3%) also had pathological Q waves. ST-T segment elevation (>0.02 mV) was found more in FHCM as compared to sporadic ($P = 0.04$). Giant T wave was present significantly higher in the sporadic form of HCM as compared to familial ($P = 0.04$). In sporadic cases, pathological Q waves were present in 97.5% of cases, whereas ST-T abnormalities were present in 90.2% of sporadic cases [Table 3].

In echocardiographic examinations, average posterior wall (PW) (LV) thickness of the HCM patients was 16 ± 4.8 mm, and interventricular septum (IVS) thickness was 21 ± 8.3 mm. Average ejection fraction (63.0 ± 8.0) was found to be normal. Mean left ventricular mass (LVM) (347.8 ± 196.9) was much higher than normal heart, details of clinical parameters are in Table 3.

FHCM patients had higher PW (LV) thickness (18.0 ± 6.3) as compared to sporadic patients (15.0 ± 4.8) whereas IVS thickness of sporadic (21 ± 7.9) was slightly higher than familial cases (20 ± 6.2). Mean LVM of familial (365.0 ± 145.4) was greater than sporadic (321.1 ± 193.5). FHCM patients had more mitral valve regurgitation and systolic anterior motion than sporadic cases [Table 3].

Sanger sequencing of hotspot region of MYH7 gene

We sequenced all 59 HCM patients and 100 clinically evaluated controls for exon 23 of MYH7 gene through Sanger sequencing and found three variants in three different families which were absent in the control group.

In one FHCM family, a rare mutation c. 2769 C > T was identified in both affected father (51 years) and affected son (16 years) along with one unaffected brother. The father had late onset of disease (48 years) as compared to son (14 years) which was due to presence of HCM associated polymorphisms in the son inherited from the mother as reported in our previous study.[19] The affected son had undergone alcohol ablation twice and the father once. We genotyped all available family members for the mutation identified and found the other son also had the mutation but still asymptomatic.

Table 2: Clinical characteristics of the HCM study population

Characteristics	Cases, *n* (%)
Symptomatic, *n* (%)	
Chest pain	36 (64.3)
Shortness of breath	35 (62.5)
Palpitation	30 (53.5)
Syncope	12 (21.4)
Presyncope	04 (07.1)
HNCM/HOCM ratio	2:1 (39/20)
Asymmetrical HCM	19 (32.2)
NYHA (III and IV)	14 (23.7)
Sudden death (*n*)	02 (3.4)
Undergone surgery/alcohol ablation/recommended ICD	13 (22.1)

HCM: Hypertrophic cardiomyopathy, HOCM: Hypertrophic obstructive cardiomyopathy, HNCM: Hypertrophic nonobstructive cardiomyopathy, NYHA: New York Heart Association, ICD: Implantable cardioverter defibrillator

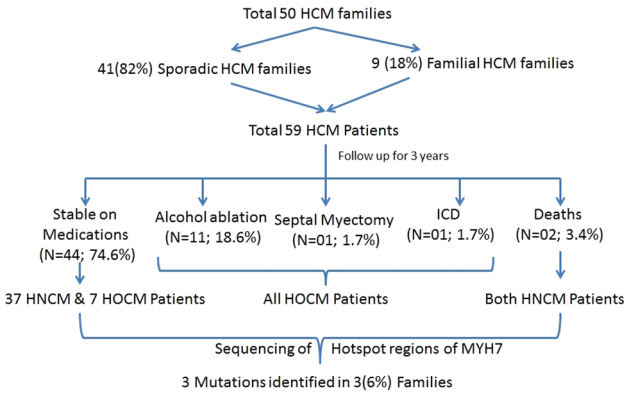

Figure 2: Summarization of results of the present study.

Table 3: ECG and echocardiography characteristics among familial and sporadic HCM patients

12-lead ECG	Total (%)	Familial (%)	Sporadic (%)	*P*
Abnormal cardiac rhythm	20 (33.9)	7 (38.8)	13 (31.7)	NS
QRS duration ≥100 ms	16 (27.1)	4 (22.2)	12 (29.2)	NS
LBBB/RBBB/LAHB	16 (27.1)	5 (27.8)	11 (26.8)	NS
ST-T abnormalities	55 (93.2)	18 (100)	37 (90.2)	NS
ST-T segment elevation ≥0.2 mV	06 (10.2)	4 (22.2)	2 (4.8)	0.04
Prolonged QTc interval	07 (11.9)	3 (16.7)	4 (9.7)	NS
Pathological Q waves	55 (93.2)	15 (83.3)	40 (97.5)	NS
Absence of normal Q wave	09 (15.2)	3 (16.7)	6 (14.6)	NS
Giant T wave	17 (28.8)	2 (11.1)	15 (36.5)	0.04
Echocardiographic assessment	**Cases (%)**			
PW (LV) thickness (mm), mean±SD	16.0±4.8	18.0±6.3	15.0±4.8	NS
IVS (mm), mean±SD	21.0±8.3	20±6.2	21±7.9	NS
LV ejection fraction (%)	63.0±8.0	62.0±8.2	63.0±8.15	NS
LVM (g)	347.8±196.9	365.0±145.4	321.1±193.5	NS
LVMI (g/m^2)	190.6±102.0	205.3±76.86	181.1±100.1	NS
MR	16 (27.1)	6 (33.3)	10 (24.3)	NS
SAM	13 (36.1)	6 (33.3)	7 (17.1)	NS

P value calculated for familial versus sporadic; *Z*-test for 12-lead ECG parameters, MR, SAM; *t*-test for echocardiographic measurements. NS: Not significant, ECG: Electrocardiography, HCM: Hypertrophic cardiomyopathy, LBBB: Left bundle branch block, RBBB: Right bundle branch block, LAHB: Left anterior hemiblock, PW: Posterior wall, LV: Left ventricle, SD: Standard deviation, IVS: Interventricular septum, LVMI: Left ventricular mass index, SAM: Systolic anterior motion, MR: Mitral valve regurgitation

In another FHCM family, a novel mutation was identified in codon 926 (C > T) changing amino acid leucine to valine. This mutation was found to occur in both affected brother (76 years) and sister (51 years) but on screening of family members, the mutation was identified in one of the sons (31 years) of the affected sister who had borderline clinical phenotype with no symptoms for HF. Both affected brother and sister had late onset (in 50 s) but sister's son was asymptomatic at 32 years. The disease expression may occur with age.

Another mutation at codon 924 (G > A) changing amino acid, glutamic acid to lysine was found in one of the sporadic HCM patients who were very young (22 years), no family history was reported and parents had died of an accident.

Treatment of hypertrophic cardiomyopathy

HCM patients are treated through various drugs to minimize the risk of sudden death or arrhythmias and other conditions which may increase disease pathogenicity. In our cohort, most of the patients (80%) were on beta blockers as first-line therapy for the management. Calcium channel blockers were administered to the 13.5% of patients. Other drugs such as statins, aspirins, and amiodarone were prescribed to patients as per the need of the patient [Figure 3].

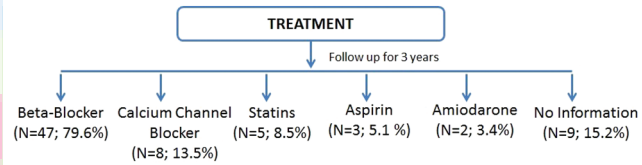

Figure 3: Distribution of treatment of hypertrophic cardiomyopathy patients.

Discussion

We studied 59 HCM patients of which there was male preponderance, nonobstructive HCM was comparatively common, and the onset was in the late 30's. Sporadic HCM was commoner, and familial type (18%) had a more severe manifestation. Hotspot sequencing picked mutations in 6% of patients.

Men are more often affected than women in HCM.[16] Our study shows preponderance of HCM in males (83.7%) with sex ratio of 5.5:1 compared to other Indian study (3.7:1),[20] Western (2.9:1),[1] and Japanese (2.3:1)[21] studies. Investigators using mouse model for FHCM, have shown lowered penetrance for the females.[22] A study using a mouse model inserted MYH7 mutations found in humans shows more pronounced electrophysiological effects in males than females.[23] It has been found that the loss of estrogen in women after menopause is strongly associated with an increase in morbidity and death from cardiovascular disease and congestive HF.[24] The role of estrogen in cardioprotection is still unclear in HCM, but mouse model studies support the notion that male sex predisposed the animal to an earlier onset and worsened cardiac phenotype than females. Females in our study were more symptomatic than males, with none in NYHA Class I; and more in NYHA Class III. A previous study by Wang *et al*., 2014 suggested the involvement of hormonal activity for worse prognosis in females.[25]

HOCM occurred less as compared to the nonobstructive type of HCM. In the previous study, it was reported that the obstructive type was the more common (approximately 70%) form of

HCM.[26,27] In the present study, HOCM was comparatively less than nonobstructive which may be due to different ethnic and environment stimuli. One of the studies suggest that patients with symptomatic nonobstructive HCM have some form of latent left ventricular outflow tract obstruction but are not expressed until stress is exerted on the LV function.[28] One of the reason may be the stress component of heart function is low in our HCM population comparable to the previously studied population due to which HOCM is not so common in this HCM population. For HOCM, both sexes have equal distribution, but out of two HOCM females, one (35 years) had a severe form showing poor prognosis for the female patients, which may be due to some hormonal changes. Wang *et al*., 2014, reported worse prognosis in female younger than 50 years but not in those with 50 years older. With nearby 96% survival, HCM patients lead near normal lives unless, they have a sudden death due to some exertion or arrhythmia.[24]

ST-T abnormalities and pathological Q waves were found in HCM patients. The presence of giant T waves was indicative of an apical form of hypertrophy. In a previous study, it was found that giant inverted T wave associated with a severe form of apical HCM.[29] FHCM patients had greater PW (LV) thickness than sporadic cases which suggest that familial form had a more severe form of the disease.

For the HCM patients, severe arrhythmia leading to sudden death are common, therefore the first line of drug for the condition is beta blockers that may prevent symptoms such as dyspnea, chest pain, and also lessen myocardial oxygen demand and decrease the outflow gradient during exercise.[12]

The genetics of inherited disorders are necessary to understand the biology of the disease. Out of 50 families studied for the MYH7, only 3 families were identified with a mutation in exon 23, which means 6% of total HCM patients. Two mutations, one (E924K) in MYH7 gene was previously reported in HCM patients[30,31] and found to be associated with HCM; and C > T at codon 923 in MYH7 gene were found to be reported in a database with HCM phenotype from South India. A novel mutation in a family (L926V) was absent in other HCM patients as well as in clinically evaluated controls suggesting a private mutation in HCM. To identify the causal mutation, we further need extensive sequencing using next generation sequencing (NGS) approach for each family as reviewed in the previous study among various cardiomyopathies.[32] With the

Table 4: Previous genetic studies for HCM in India

Study	Patients	Brief detail of study
Waldmüller *et al*., 2003[34]	12 HCM families	Screened MYH7 and MYBPC3 gene and found novel deletion in both genes associated with HCM in families
Annapurna *et al*., 2007[35]	92 HCM	SSCP followed by sequencing of troponin I (TNNI3) gene, a one synonymous mutation at exon 5 and two intronic mutations in 3 patients
Bashyam *et al*., 2012[36]	1 HCM family	A p.R870H mutation in MYH7 gene causes FHCM in several members with clinical heterogeneity
Rai *et al*., 2008[37]	118 HCM, 51 DCM, 5 RCM	D allele of ACE (I/D) is significantly higher in HCM patients (D allele = 0.64) with ID had higher spetal thickness as compared to other genotype
Tanjore *et al*., 2008[20]	95 HCM	Screened exons of 16, 18, 19, 22, 24, 28, 30, 31 and 34 in the MYBPC3 gene and revealed two variations - one novel frameshift mutation (nt11577-78) in exon 19 and one novel SNP in codon 1093
Rai *et al*., 2009[38]	69 HCM	Reported 5 mutations out of which three novel mutations and one known mutation (Gly716Arg) resulted in severe asymmetric septal hypertrophy
Dhandapany *et al*., 2009[39]	800 HCM	25bp deletion of MYBPC3 gene was associated with increased risk of heritable cardiomyopathies and was found to common risk factor for South Asian populations
Rao *et al*., 2011[40]	150 HCM	Significant difference was found in genotypic distribution as well as for allelic frequency of M235T of exon 5 in AGT gene between HCM patients and controls
Bashyam *et al*., 2012[36]	55 HCM	Showed that MYBPC3 mutations had a greater frequency of occurrence than MYH7. Reported 12 patients in MYBPC3 while 5 in MYH7
Rani *et al*., 2012[41]	162 HCM	Sequenced TNNT2 gene revealed 15 variants including 5bp Del in intron 3 which skips exon 4, was highly polymorphic and associated with HCM
Rani *et al*., 2012[42]	101 HCM	Sequenced TNNI3 gene, observed 16 mutations and interestingly found that R to Q mutation 3 positions 98,141 and 162 and patient carrying those mutation had severe phenotype or lead to sudden death
Rangaraju *et al*., 2012[43]	100 HCM	Coding regions of cardiac LIM protein genes (ACTC and CLP) were sequenced but could not identify exonic mutation
Biswas *et al*., 2012[19]	One HCM family	Reported a MYH7 mutation segregating in the family with other modifier polymorphism to address clinical heterogeneity
Govindaraj *et al*., 2014[44]	114 HCM	Complete mtDNA analysis revealed 28 variations, 25 diseases associated and 50 private mutations out of which 13 (11.4%) HCM patients had novel nonsynonymous or/and Mt-tRNA variations
Selvi Rani *et al*., 2015[45]	101 HCM, 147 DCM	Found that coexistence of digenic mutations in both thin (TPM1) and thick (MYH7) filaments of sarcomeric genes had severe phenotype
Present study, 2015	50 HCM families	Clinical details (ECG and echocardiography) of patients followed up for 3 years to track the record of the patients with treatment details. Differences between familial and sporadic HCM patients. Sequencing of hotspot regions of MYH7

HCM: Hypertrophic cardiomyopathy, DCM: Dilated cardiomyopathy, RCM: Restrictive cardiomyopathy, SSCP: Single stranded conformation polymorphism technique, FHCM: Familial hypertrophic cardiomyopathy, ECG: Electrocardiography

advent of NGS, mutations from various genes are identified which necessitate for the *in silico* analysis.[33] Previous genetics studies conducted in the Indian cohort have been briefly summarized in Table 4.

Conclusion

HCM is a genetic disorder being more prevalent in males. The occurrence of HNCM was more as compared to HOCM. Around 18% of cases are familial and the rest are considered to be sporadic. FHCM patients had early onset of disease as compared to sporadic. With greater PW (LV) thickness, FHCM had a more severe form of the disease than sporadic. Genetic screening of hotspot region of MYH7 only explains 6% of the genetic basis, probably more extensive, and holistic approach to whole genome or whole exome sequencing may reveal the causal genes associated with disease pathogenesis.

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Conflicts of interest

There are no conflicts of interest.

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