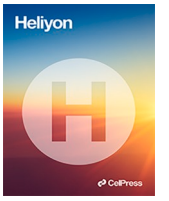
Heliyon 10 (2024) e34727

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

MYH7 mutation is associated with mitral valve leaflet elongation in patients with obstructive hypertrophic cardiomyopathy

Xinli Guo [a,1], Manyun Huang [b,1], Changpeng Song [a], Changrong Nie [c], Xinxin Zheng [a], Zhou Zhou [a], Shuiyun Wang [c], Xiaohong Huang [a,*]

[a] Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences, Peking Union Medical College, 167 Beilishilu, Beijing, 100037, China
[b] Department of Heart Failure, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, 200120, China
[c] Department of Cardiovascular Surgery, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences, Peking Union Medical College, 167 Beilishilu, Beijing, 100037, China

ARTICLE INFO

Keywords:
Obstructive hypertrophic cardiomyopathy
MYH7 gene variation
Mitral valve leaflet elongation
Cardiac magnetic resonance imaging

ABSTRACT

Mitral valve (MV) leaflet elongation is recognized as a primary phenotypic expression of hypertrophic cardiomyopathy (HCM) that contributes to obstruction. This study investigates the correlation between MV length and genotype mutations in the two predominant genes, myosin-binding protein C (MYBPC3), and the β-myosin heavy chain (MYH7) in patients with obstructive HCM (OHCM). Among the 402 OHCM patients, there were likely pathogenic or pathogenic variations in MYH7 (n = 94) and MYBPC3 (n = 76), along with a mutation-negative group (n = 212). Compared to genotype-negative patients, genotype-positive individuals exhibited elongated MV length, thicker interventricular septum, and increased instances of late gadolinium enhancement. Notably, MYH7 mutations were associated with a more severe disease trajectory than MYBPC3 mutations. After adjusting for potential confounders, multivariate linear regression analysis revealed that MYH7 gene mutations and left ventricular volume were independently associated with MV leaflet elongation. The study indicates that mutations in MYH7 and hemodynamics factors are significant risk factors for elongated MV leaflet. Consequently, regular assessment of MV length, especially in patients with MYH7 mutation and enlarged LV volume, is crucial for timely preoperative strategic planning and improved prognosis.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiomyopathy, with a prevalence of 1 in 200 to 1 in 500 in the general population, primarily characterized by left ventricular (LV) hypertrophy [1–3]. The major HCM-associated mutations identified to date are the myosin-binding protein C (MYBPC3) and the β-myosin heavy chain (MYH7) genes [4], both of which affect the thick filament of the sarcomere [5] through distinct pathways. Current literature suggests that MYH7 mutations are associated with earlier onset [6–8] and more severe disease trajectory compared to MYBPC3 mutations [5,9]. However, not all studies confirm this association [10–12].

* Corresponding author.
E-mail address: huangxiaohong@fuwaihospital.org (X. Huang).
[1] These two authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e34727
Received 26 February 2024; Received in revised form 20 June 2024; Accepted 15 July 2024
Available online 16 July 2024

Recent research has observed that mitral valve (MV) abnormalities are common in patients with HCM, including MV leaflet elongation and irregular subvalvular structures [13]. These deviations often precipitate the onset of left ventricular outflow tract obstruction (LVOTO), subsequently leading to clinical manifestations and adverse events. The precise relationship between MV leaflet elongation and sarcomeric gene mutations is in dispute. Some researchers attribute elongation primarily to genotype-positive patients [14], while others believe that LV remodeling, body size [15], chamber geometry, and hypertrophy pattern [16] are more significant factors than genetics. Additionally, some studies have found no significant differences in MV length and phenotypes between MYH7+ and MYBPC3+ associated HCM [12]. Therefore, it remains unclear whether mitral leaflet elongation in HCM patients mainly depends on genotype or on additional geometric or hemodynamic factors.

Given the contradictory and limited insights into MV leaflet elongation in obstructive HCM (OHCM), this study aims to elucidate the correlation between MV length and mutations in the two prevalent genes, MYH7 and MYBPC3. Moreover, we seek to identify the risk factors influencing MV length.

2. Methods

2.1. Study population

We enrolled 422 patients with OHCM from Beijing Fuwai Hospital between 2010 and 2019, all of whom were slated for septal myectomy treatment and underwent both genetic testing and preoperative echocardiography imaging, as well as cardiac magnetic resonance imaging (CMR) examination. Of these, 402 patients with pathogenic mutation in either MYBPC3 or MYH7 genes, or who were genotype-negative, were included in the analysis. All patients met the diagnostic criteria of the American College of Cardiology and the American Heart Association [2], which include: Ventricular septum or left ventricular wall thickness $\geq$15 mm, or thickness $\geq$13 mm with family history, usually not accompanied by left ventricular enlargement, and left ventricular wall thickening caused by increased left ventricular afterload needs to be excluded. The exclusion criteria are as follows: (1) patients with connective tissue disease, mitral valve stenosis, previous cardiac surgery, mitral regurgitation caused by congenital or ischemic heart disease, pericardial and myocardial diseases; (2) Patients with tumors, autoimmune diseases, severe renal failure, or serious infection; (3) Incomplete medical records. This study was approved by the institutional review board at Fuwai hospital, with ethics approval reference [2022-1892]; informed consent was obtained from all participants.

2.2. Genetic testing and analysis

Peripheral venous blood was collected from patients for gene sequencing using the Panel sequencing method from NimbleGen (Roche, Basel, Switzerland), which included 93 genes associated with cardiomyopathy and related syndromes. We specifically screened eight sarcomere genes definitively associated with HCM: myosin binding protein C (MYBPC3), myosin heavy chain (MYH7), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), α-tropomyosin (TPM1), myosin essential and regulatory light chains (MLY2, MYL3), and actin (ACTC). Additionally, we screened 85 other genes related to cardiomyopathy and related syndromes. Variants were categorized based on the standards set by the American College of Medical Genetics and Genomics as pathogenic (P), likely pathogenic (LP), of unknown significance (VUS), likely benign (LB), or benign (B) [17]. A positive genotype included patients exhibiting P/LP gene variants, while a negative genotype (G-) encompassed patients without the eight common mutations or with VUS/LB/B variants.

2.3. Echocardiography

A comprehensive echo-Doppler evaluation was performed according to current American Society of Echocardiography guidelines [18]. The standard echocardiography study measured systolic and diastolic parameters, including left atrial (LA) diameter, LV end-diastolic diameter (LVEDD), and LV ejection fraction (LVEF). Continuous wave Doppler was used to measure the peak velocity across the LVOT, and the pressure gradient was calculated using the Bernoulli equation: $4 \times (\text{peak velocity across the LVOT})^2$ [19]. Systolic anterior motion (SAM) was evaluated by visual assessment on both the parasternal long-axis and apical long-axis 2D echocardiography. SAM was defined as the systolic anterior motion of the body of the anterior leaflet of the mitral valve and/or of the mitral valve chordae tendineae into the LVOT.

2.4. Cardiac magnetic resonance imaging

CMR was conducted at Fuwai hospital using standard clinical scans on either a 1.5 or 3.0 T MRI scanner for all recruited patients. All imaging acquisitions were performed under electrocardiographically-gated and breath control. The CMR protocol included obtaining standard long-axis cine images and sequential 8-mm short-axis slices from atrium to apex using a steady-state free precession sequence. Cine scans in multiple short-axis and three long-axes views (2-chamber, 4-chamber, and LVOT) were acquired by using a True imaging with steady-stage precession (TrueFISP) sequence. CMR image analysis, including LV mass, LV volume, and LV function, was performed on a commercial imaging workstation (Siemens Medical Systems). After intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Magnevist, Schering, Berlin, Germany) for 15 min, late gadolinium enhancement (LGE) images were acquired using a breath-held phase-sensitive segmented inversion-recovery sequence in the same views as the cine images, both in short-axis and long-axis views. LGE-positive was defined as visible areas showing increased signal intensity relative to surrounding tissues after the administration of gadolinium-DTPA.

2.5. Image analyses

The lengths of the anterior mitral leaflet (AML) and posterior mitral leaflet (PML) were measured during diastole using the method described by Maron et al. [14]. This measurement was specifically conducted in the 3-chamber view, where the leaflets maximally extended parallel to the anterior septum and LV free wall. The 3-chamber view was derived from the slice plane oriented along the aortic root parallel to the LV outflow tract. Leaflet length was defined as the distance from the most distal extent of anterior leaflet to its insertion into the posterior aortic wall, and similarly, from the most distal extent of the posterior leaflet into the basal LV posterior free wall. MV lengths were measured independently by two physicians who were blind to the patients' clinical situation. Given the strong correlation between leaflet length and body surface area (BSA) established in previous studies, these measurements were adjusted for body size by dividing by BSA to eliminate this influence [16].

Table 1
Baseline characteristics in OHCM patients among three groups.

Characteristics	G- (n = 232)	MYPBC3+ (n = 76)	MYH7+ (n = 94)	*P*-value for global test
Demographic characteristics				
Age at diagnose, years	47.1 ± 14.5	36.4 ± 13.4	34.9 ± 13.8	<0.001[a,b]
Male,n	142 (61.2)	59 (77.6)	54 (57.4)	0.014[a,c]
Duration, years	5.3 ± 8.8	4.2 ± 5.0	4.4 ± 4.5	0.373
Smoking,n	90 (38.8)	31 (40.8)	28 (29.8)	0.237
Alcohol,n	66 (28.4)	15 (19.7)	14 (14.9)	0.022[b]
BMI kg/m^2	25.3 ± 3.6	24.1 ± 3.9	24.1 ± 4.2	0.015[b]
BSA,m^2	1.8 ± 0.2	1.8 ± 0.2	1.7 ± 0.2	0.043[c]
SBP, mmHg	123.7 ± 16.3	122.2 ± 15.0	118.0 ± 14.0	0.010[b]
DBP, mmHg	74.0 ± 10.9	71.5 ± 10.3	69.4 ± 9.8	0.001[b]
HR, beats	72,5 ± 9.3	74.2 ± 8.4	69.4 ± 9.8	0.201
NYHA III-IV,n	109 (47.0)	26 (34.2)	39 (41.5)	0.138
Family history	28 (12.1)	18 (23.7)	22 (23.4)	0.010[a,b]
Comorbidity,n				
Hypertension	81 (34.9)	13 (17.1)	8 (8.5)	<0.001[a,c]
Diabetes	9 (3.9)	1 (1.3)	1 (1.1)	0.259
Hyperlipidemia	76 (32.8)	14 (18.4)	18 (19.1)	0.008[b]
Coronary heart disease	25 (10.8)	1 (1.3)	1 (1.1)	0.001[a,b]
Atrial fibrillation	30 (12.9)	1 (1.3)	13 (13.8)	0.011[a,c]
Medication,n				
β-Blocker	225 (97.0)	75 (98.7)	89 (94.7)	0.327
CCB	68 (29.3)	20 (26.3)	19 (20.2)	0.242
Diuretics	43 (18.5)	10 (13.2)	10 (10.6)	0.165
ACEI/ARB	46 (19.8)	9 (11.8)	4 (4.3)	<0.001[b]
Echocardiography parameters				
LAD, mm	44.5 ± 7.0	42.4 ± 6.7	45.2 ± 7.2	0.016[a,c]
LVEDD, mm	42.9 ± 5.0	41.6 ± 6.6	41.0 ± 5.6	0.012[b]
Rest LVOT gradient, mmHg	73.5 ± 37.7	63.9 ± 30.7	66.8 ± 31.4	0.068
MR (mid-massive)	113 (48.9)	25 (32.9)	43 (46.5)	0.050[a]
SAM	211 (91.3)	73 (96.1)	88 (94.6)	0.295
CMR values				
IVS, mm	24.9 ± 5.8	30.1 ± 6.6	26.5 ± 5.7	<0.001[a,b,c]
LVESVi, ml/m^2	29.3 ± 13.1	31.3 ± 10.4	28.8 ± 10.2	0.344
LVEDVi, ml/m^2	83.0 ± 22.8	84.8 ± 19.4	81.6 ± 18.4	0.629
LVEF, %	66.0 ± 8.7	63.5 ± 7.0	64.5 ± 8.4	0.048[a]
LVMassi, g/m^2	101.2 ± 44.6	114.6 ± 45.9	99.3 ± 42.2	0.045[a]
Presence of LGE,n	179 (82.5)	73 (96.1)	88 (97.8)	<0.001[a,b]
AML length,mm	24.3 ± 4.6	25.5 ± 4.2	26.2 ± 4.5	0.002[b]
PML length,mm	11.8 ± 2.7	13.0 ± 2.5	13.0 ± 3.1	<0.001[a,b]
iAML length,mm/m^2	13.9 ± 2.8	14.4 ± 2.8	15.5 ± 3.4	<0.001[b,c]
iPML length,mm/m^2	6.7 ± 1.7	7.4 ± 1.7	7.7 ± 2.1	<0.001[a,b]

Abbreviation: OHCM obstructive hypertrophic cardiomyopathy; BMI body mass index; BSA body surface area; SBP systolic blood pressure; DBP diastolic blood pressure; HR heart rate; NYHA, New York Heart Association; CCB, calcium channel blocker; ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LV, left ventricular; EF, ejection fraction; IVS, interventricular septal; LVOT, left ventricular outflow tract; CO cardiac output; EDVi end-diastolic volume index; ESVi end-systolic volume index; LGE, late gadolinium enhancement; CMR cardiac magnetic resonance; AML, anterior mitral leaflet; PML, posterior mitral leaflet; iAML, AML/BSA); iPML, PML/BSA.

[a] P-value<0.05, G-vs. MYPBC3+.

[b] P-value<0.05, G-vs. MYH7+.

[c] P-value<0.05, MYH7 vs. MYPBC3+.

2.6. Statistical analysis

Continuous variables with normal distributions were presented as mean ± standard deviation, while categorical variables were reported as percentages. Baseline features were compared among the three patient groups (MYH7+, MYBPC3+, or G-) using ANOVA or the $\chi 2$ test as appropriate. Univariate and multivariate linear regression analyses were conducted to investigate the impact of genotype on MV length. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS Statistics software (version 21.0; IBM Corp.), and figures were generated using GraphPad Prism (version 8.0).

3. Results

3.1. Baseline characteristics

In this study of 422 patients who under genetic testing, 190 patients (45.0 %) tested positive for pathogenic mutations. The most frequently observed mutations were in MYH7 (n = 94, 49.5 %) and MYBPC3 (n = 76, 40.0 %). Table 1 outlines the baseline characteristics among G-, MYPBC3+ and MYH7+ groups. The median age of the cohort was 42.3 years, with a majority being male (n = 255, 63.4 %). Patients with MYBPC3 and MYH7 mutations were significantly younger and more frequently had a history of familial hypertrophic heart disease compared to those without gene mutations ($p < 0.05$). G-patients exhibited a higher prevalence of hypertension, hyperlipidemia, and coronary heart disease, along with greater weight and were more frequent use of ACEI/ARB medications. Furthermore, patients with MYH7 mutations had a lower BSA, fewer cases of hypertension, but a higher incidence of atrial fibrillation compared to those in the MYBPC3+ group.

3.2. Genotype-to-phenotype correlations

Significant differences in cardiac structure and function were observed among the groups. Both the MYH7+ and MYPBC3+ groups exhibited significantly thicker IVS compared to the G-group ($p < 0.001$). Specifically, the MYH7+ group showed a significantly greater LAD measured by echocardiography, which was notably higher than the other two groups. Additionally, there was a trend towards smaller LVEDD measured by echocardiography in the MYH7+ and MYBPC3+ groups. CMR-derived LVEF values were marginally lower in mutation-positive individuals ($p = 0.048$) compared to the control cohort. There was no discernible differences in parameters such as rest LVOT gradient, SAM, cardiac output, LVESVi, and LVEDVi among the three groups. The presence of LGE was more prevalent in both MYH7+ and MYPBC3+ groups compared to the G-group. Furthermore, the MV leaflet lengths in the mutation-positive cohorts were greater than those in the G-group (AML: 25.5 ± 4.2, 26.2 ± 4.5 VS 24.3 ± 4.6 mm; PML: 13.0 ± 2.5, 13.0 ± 3.1 VS 11.8 ± 2.7 mm; both $P < 0.001$), even after adjusting for BSA (Table 1 and Fig. 1).

3.3. The risk factors for MV length

Table 2 presents the results of univariate linear regression analysis for MV leaflet length. According to the univariate analysis, demographic characteristics such as age, blood pressure, presence of hypertension, genetic mutations, geometric parameters, presence of LGE, and hemodynamic factors including LVEDVi, LVESVi, and LVEF, were all significantly associated with MV leaflet length. In the multivariate analysis, after adjusting for demographic characteristics such as gender, age, hypertension, geometric and hemodynamic parameters, and the present of LGE, the MYH7 gene mutation emerged as a consistent risk factor for elongated anterior and posterior

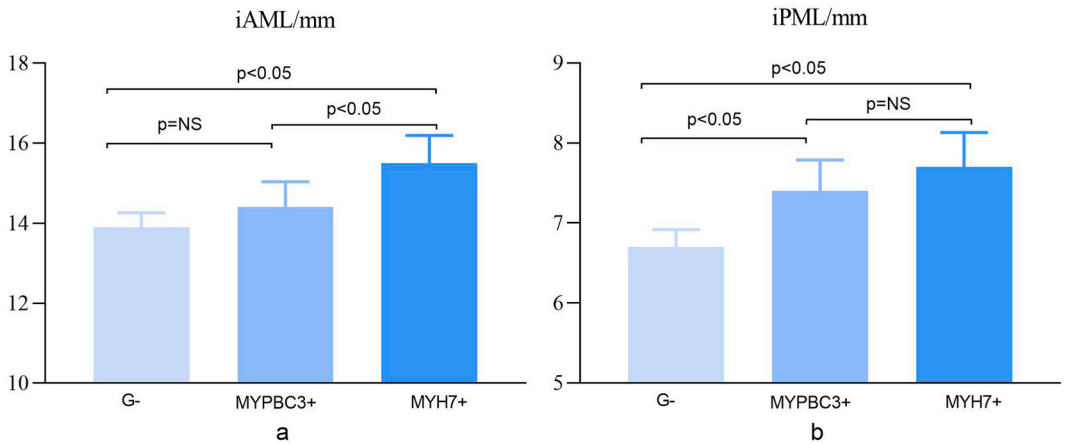


Fig. 1. Analysis of the MV leaflet length among G-(light blue), MYBPC3+ (mid blue), and MYH7+ (dark blue) groups. MV leaflet length, including indexed anterior mitral leaflet (iAML: AML/BSA) and indexed posterior mitral leaflet (iPML: PML/BSA), was significantly higher in the MYH7+ group compared to both MYBPC3+ and the G-group ($P < 0.05$).

Table 2
Univariate linear analysis of iAML and iPML.

Parameters	iAML				iPML			
	b	se	t	P	b	se	t	P
Age	−0.048	0.010	−4.924	<0.001	−0.031	0.006	−5.439	<0.001
Female	0.998	0.310	3.223	<0.001	0.318	0.188	1.688	0.092
Genotype								
G-	Ref.			1.000	Ref.			1.000
MYPBC3+	0.039	0.386	0.100	0.193	0.622	0.235	2.648	0.008
MYH7+	1.508	0.349	4.325	<0.001	0.985	0.217	4.530	<0.001
BMI	−0.347	0.035	−9.922	<0.001	−0.195	0.021	−9.116	<0.001
SBP ≤120 mmHg	1.348	0.297	4.541	<0.001	0.565	0.181	3.113	0.002
DBP ≤70 mmHg	0.723	0.300	2.409	0.016	0.582	0.180	3.234	0.001
HR	0.022	0.016	1.356	0.176	0.002	0.010	0.160	0.873
smoking	−0.880	0.310	−2.844	0.005	−0.335	0.188	−1.784	0.075
Drinking	−0.499	0.355	−1.407	0.160	−0.110	0.214	−0.512	0.609
Hypertension	−1.738	0.336	−5.173	<0.001	−0.884	0.204	−4.321	<0.001
Family history	0.563	0.402	1.401	0.162	0.331	0.242	1.367	0.172
Echocardiography parameters								
LAD	−0.010	0.021	−0.463	0.644	−0.023	0.013	−1.823	0.069
LVEDD	−0.115	0.027	−4.267	0.001	−0.038	0.017	−2.293	0.022
SAM	−0.363	0.592	−0.613	0.540	−0.218	0.358	−0.608	0.544
Rest LVOT gradient	0.006	0.004	1.351	0.178	−0.003	0.003	−1.133	0.258
MR (mid-massive)	0.762	0.301	2.531	0.012	0.262	0.183	1.432	0.153
CMR values								
IVS	0.050	0.024	2.070	0.039	0.044	0.014	3.087	0.002
LVESVi	0.041	0.012	3.313	0.001	0.022	0.008	2.962	0.003
LVEDVi	0.021	0.007	3.007	0.003	0.015	0.004	3.471	0.001
LVEF	−0.048	0.018	−2.706	0.007	−0.018	0.011	−1.680	0.094
LVMassi	0.008	0.003	2.350	0.019	0.006	0.002	2.774	0.006
LGE	1.323	0.472	2.803	0.005	0.778	0.289	2.692	0.007

Abbreviations are summarized in Table 1.

leaflets length (OR: 2.286, 95 % CI: 1.158–4.514, p = 0.018; OR: 1.611, 95 % CI: 1.055–2.460, p = 0.028, separately). Additionally, LV volume was also significantly associated with elongation of MV leaflet. Detailed findings are presented in Table 3.

4. Discussion

To our knowledge, this is the first study to comprehensively investigate the effect of sarcomere gene mutations on MV leaflet elongation in patients with OHCM. The key findings are as follows: (i) Patients with MYH7+ and MYPBC3+ associated OHCM display longer MV leaflets, thicker IVS, and a higher incidence of LGE compared to G-patients. (ii) Among mutation carriers, those with MYH7 mutations exhibit a more severe disease trajectory than those with MYBPC3 mutations, including more pronounced MV length elongation. (iii) Both MYH7 mutations and LV volume significantly impact MV length, even after controlling for other factors.

The precise pathogenesis of MV leaflet elongation in patients with HCM remains uncertain. Recently, an increasing number of studies have recognized the role of gene mutation in this pathology [14,20]. John D. Groarke et al. compared the MV length of 192 participants and concluded that the MV length in gene-positive HCM patients was significantly longer than that in mutation-negative and subclinical group [21]. Additionally, healthy carriers without echocardiographic evidence of LV hypertrophy also exhibit pathologic elongation of the AML [14], which suggests that the MV elongation represents an independent and primary phenotypic expression in genotype-positive patients with HCM. Our study expands on this knowledge by focusing on patients with HOCM. We found that patients with sarcomere mutations commonly exhibit elongated MV leaflets, consist with previous studies. However, to our knowledge, the sarcomere genes are expressed exclusively in cardiac muscle, with no evidence of expression in heart valves [22,23]. A developmental hypothesis suggests that elongation of MV is due to paracrine effects arising in the adjacent hypertrophic ventricle [24],

Table 3
Multivariate linear analysis of iAML and iPML[a].

Parameters	iAML				iPML			
	B	SE	OR (95%CI)	*P*	B	SE	OR (95%CI)	*P*
Genotype								
G-	Ref.			1.000	Ref.			1.000
MYPBC3+	0.241	0.387	1.273 (0.600–2.717)	0.534	0.403	0.235	1.496 (0.944–2.372)	0.087
MYH7+	0.827	0.347	2.286 (1.158–4.514)	0.018	0.477	0.216	1.611 (1.055–2.460)	0.028
LVEDVi	…	…	…	…	0.013	0.004	1.013 (1.005–1.021)	0.003
LVESVi	0.031	0.012	1.031 (1.008–1.056)	0.009	…	…	…	…

[a] The multivariate model was adjusted for age, gender, smoking, hypertension, LAD, IVS, LVEDVi, LVESVi, LVEF, LVMassi and LGE.

though this has not yet been proven. Consequently, future longitudinal studies in both human and animal models of HCM with MV disease are warranted to better understand the etiology.

In this study, we found that patients with causal MYH7 variants exhibit more severe features than those with MYPBC3 mutations. In fact, accumulating evidence supports that MYH7 mutations are associated with earlier disease onset, more severe phenotypes, and worse prognosis, including increased frequency of AF [25,26], higher degree of mitral regurgitation (MR) [11], and enlarged LAD [25], aligning with our results. Regarding the correlation between the LV wall hypertrophy and genotype, our results show a statistically significant trend of higher IVS measurements in the MYPBC3+ group, consistent with previous observations [11]. However, a multicenter multinational study by Adaya et al. found no phenotypic differences between patients with MYH7 and MYBPC3 mutations when assessed by CMR, including LGE extent and MV length. This discrepancy might be due to the inclusion of only patients with similar HCM phenotypes [12]. The MYH7 gene encodes the cardiac heavy chain protein, crucial for muscle contraction, with missense mutations producing abnormal proteins and causing severe myocardial structural and functional impairments [23,27,28]. On the other hand, cardiac MYBPC regulates myocardial contractility, with truncating mutations usually resulting in reduced production or loss of function of the protein, thereby having a relatively smaller impact on cardiac function [29]. Consequently, the phenotypic differences described above are often attributed to the functional differences between the proteins coded by these genes [11,30] and the more severe disturbance in myocardial efficiency caused by MYH7 mutations compared to MYBPC3 mutations [31].

Based on current data and historical observations, disease-causing mutations in cardiac sarcomere proteins are unlikely to fully account for the entire phenotypic expression of HCM, with other factors like hemodynamic parameters potentially contributing to specific morphological abnormalities, including MV elongation [32]. Previous research has traditionally attributed MV leaflet elongation to heart geometry or hemodynamics [33,34]. In an animal study conducted by Manuel K. Rausch et al. involving five adult sheep, it was concluded that adaptive mitral leaflet growth can be induced by hemodynamic load [35]. Similarly, Hyemoon Chung et al. observed the significant and independent correlations between MV leaflet size and the degree of MR and geometry parameters, including LV volume, LV mass, and diastolic MV wall stress index from the left atrial side in patients with HCM, while no independent relationships with genetic factors were found [16]. We found that LV volume is a risk factor potentially leading to annular dilation and elongation of the MV leaflets, despite its odds ratio being relatively smaller compared to MYH7 gene mutations. The mechanism may involve the mechanical stretching of the valve apparatus during left ventricular remodeling and the occurrence of SAM. These morphological alterations change the direction of the LV blood flow, causing the high-speed blood flow to repeatedly hit the anterior mitral leaflet and push it forward, ultimately resulting in the MV leaflet elongation.

MV elongation is common in patients with OHCM, yet its relationship with specific gene mutations has not been fully explored. This research addresses this gap, providing new insights into the role of gene mutations in cardiac pathology and highlighting the influence of both genotype and hemodynamic parameters on MV elongation. Increased MV length is one of the significant determinants of LVOT in patients with HCM [36,37], with obstruction contributing to progressive LV diastolic dysfunction, heart failure, and the risk of sudden death [38]. Therefore, the findings of this study have crucial implications for clinical management and prognosis. Regular follow-up and monitoring of MV condition in patients with MYH7 gene mutations are particularly essential to ensure timely and appropriate treatment and intervention. A combined approach of septal myectomy and AML repair has been widely reported to improve hemodynamic outcomes and prognosis in severely symptomatic OHCM patients [39,40]. Consequently, CMR assessment of MV length and LV volume, especially in patients with MYH7 mutation, may play a significant role in preoperative strategic planning. This approach can help to identify patients where MV size and leaflet length could impact surgical management. Finally, personalized treatment strategies should take into account the patient's genetic background, cardiac morphology, and functional characteristics to optimize therapeutic outcomes and improve prognosis.

Our study had some limitations. Firstly, its retrospective design and potential patient bias, conducted at a single center, may affect the findings. However, given the relative rarity of HCM, the inclusion of 402 patients represents a considerable dataset. Secondly, we only examined the patients with OHCM, which may limit the generalizability of our findings. The impact of MYH7 mutations in OHCM at earlier stages still needs further investigation. Moreover, while we adjusted for several confounding factors, there may still be residual confounders that were not accounted for in our analysis. Finally, although we concluded MV elongation results from both MYH7 mutations and hemodynamic factors, the underlying growth process remains unclear. Further rigorous experimental studies are needed to elucidate the concrete process and the potential mechanisms involved.

5. Conclusions

In summary, our data suggest that both the MYH7 gene mutation and LV volume contribute to the MV leaflet elongation. MYH7 carriers, particularly those with increased LV volume, may be at elevated risks for elongated MV leaflet. Further research with larger cohorts of HCM across various gene mutations will be essential to solidify these findings.

Data availability statement

Data will be made available on reasonable request.

CRediT authorship contribution statement

Xinli Guo: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Manyun Huang:** Writing – original draft, Software, Methodology, Investigation, Data curation, Conceptualization. **Changpeng Song:** Writing – review & editing,

Formal analysis, Data curation. **Changrong Nie:** Writing – review & editing, Investigation, Data curation. **Xinxin Zheng:** Validation, Supervision. **Zhou Zhou:** Validation, Data curation. **Shuiyun Wang:** Writing – review & editing, Validation, Data curation, Conceptualization. **Xiaohong Huang:** Writing – review & editing, Visualization, Validation, Supervision, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We appreciate the effort of all clinical physicians and researchers who contributed to this work, as well as the understanding and support of the patients. This work was supported by grants from the the National High Level Hospital Clinical Research Funding of China (grant number 2022-GSP-TS-8).

References

[1] P.M. Elliott, A. Anastasakis, M.A. Borger, et al., ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC), Eur Heart J 2014 35 (2014) 2733–2779.
[2] B.J. Gersh, B.J. Maron, R.O. Bonow, et al., 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines, Circulation 124 (2011) 2761–2796.
[3] B.J. Maron, Hypertrophic cardiomyopathy: a systematic review, JAMA 287 (2002) 1308–1320.
[4] J.M. Bos, J.A. Towbin, M.J. Ackerman, Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 54 (2009) 201–211.
[5] L. Velicki, D.G. Jakovljevic, A. Preveden, et al., Genetic determinants of clinical phenotype in hypertrophic cardiomyopathy, BMC Cardiovasc. Disord. 20 (2020) 516.
[6] B. Adalsteinsdottir, M. Burke, B.J. Maron, et al., Hypertrophic cardiomyopathy in myosin-binding protein C (MYBPC3) Icelandic founder mutation carriers, Open Heart 7 (2020) e001220.
[7] J.B. Geske, K.C. Ong, K.C. Siontis, et al., Women with hypertrophic cardiomyopathy have worse survival, Eur. Heart J. 38 (2017) 3434–3440.
[8] M. Sabater-Molina, I. Pérez-Sánchez, J.P. Hernández Del Rincón, J.R. Gimeno, Genetics of hypertrophic cardiomyopathy: a review of current state, Clin. Genet. 93 (2018) 3–14.
[9] F. Sedaghat-Hamedani, E. Kayvanpour, O.F. Tugrul, et al., Clinical outcomes associated with sarcomere mutations in hypertrophic cardiomyopathy: a meta-analysis on 7675 individuals, Clin. Res. Cardiol. 107 (2018) 30–41.
[10] L.R. Lopes, M.S. Rahman, P.M. Elliott, A systematic review and meta-analysis of genotype-phenotype associations in patients with hypertrophic cardiomyopathy caused by sarcomeric protein mutations, Heart 99 (2013) 1800–1811.
[11] S. Waldmüller, J. Erdmann, P. Binner, et al., Novel correlations between the genotype and the phenotype of hypertrophic and dilated cardiomyopathy: results from the German Competence Network Heart Failure, Eur. J. Heart Fail. 13 (2011) 1185–1192.
[12] A. Weissler-Snir, W. Hindieh, C. Gruner, et al., Lack of phenotypic differences by cardiovascular magnetic resonance imaging in MYH7 (β-myosin heavy chain)-versus MYBPC3 (Myosin-Binding protein C)-Related hypertrophic cardiomyopathy, Circ Cardiovasc Imaging 10 (2017).
[13] S. Sakellaropoulos, S. Svab, M. Mohammed, et al., The role of mitral valve in hypertrophic obstructive cardiomyopathy: an updated review, Curr. Probl. Cardiol. 46 (2021) 100641.
[14] M.S. Maron, I. Olivotto, C. Harrigan, et al., Mitral valve abnormalities identified by cardiovascular magnetic resonance represent a primary phenotypic expression of hypertrophic cardiomyopathy, Circulation 124 (2011) 40–47.
[15] M. Tarkiainen, P. Sipola, M. Jalanko, et al., Cardiovascular magnetic resonance of mitral valve length in hypertrophic cardiomyopathy, J. Cardiovasc. Magn. Reson. 18 (2016) 33.
[16] H. Chung, Y. Kim, C.H. Park, et al., Genetic relevance and determinants of mitral leaflet size in hypertrophic cardiomyopathy, Cardiovasc. Ultrasound 17 (2019) 21.
[17] S. Richards, N. Aziz, S. Bale, et al., Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for molecular Pathology, Genet. Med. 17 (2015) 405–424.
[18] R.M. Lang, L.P. Badano, V. Mor-Avi, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. 28 (2015) 1–39.e14.
[19] Z. Sasson, P.G. Yock, L.K. Hatle, et al., Doppler echocardiographic determination of the pressure gradient in hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 11 (1988) 752–756.
[20] G. Captur, L.R. Lopes, T.J. Mohun, et al., Prediction of sarcomere mutations in subclinical hypertrophic cardiomyopathy, Circ Cardiovasc Imaging 7 (2014) 863–871.
[21] J.D. Groarke, P.Z. Galazka, A.L. Cirino, et al., Intrinsic mitral valve alterations in hypertrophic cardiomyopathy sarcomere mutation carriers, Eur Heart J Cardiovasc Imaging 19 (2018) 1109–1116.
[22] L. Carrier, G. Mearini, K. Stathopoulou, F. Cuello, Cardiac myosin-binding protein C (MYBPC3) in cardiac pathophysiology, Gene 573 (2015) 188–197.
[23] A.J. Marian, Molecular genetic basis of hypertrophic cardiomyopathy, Circ. Res. 128 (2021) 1533–1553.
[24] A.A. Hagège, P. Bruneval, R.A. Levine, et al., The mitral valve in hypertrophic cardiomyopathy: old versus new concepts, J Cardiovasc Transl Res 4 (2011) 757–766.
[25] J.D. Marsiglia, F.L. Credidio, T.G. de Oliveira, et al., Screening of MYH7, MYBPC3, and TNNT2 genes in Brazilian patients with hypertrophic cardiomyopathy, Am. Heart J. 166 (2013) 775–782.
[26] S.P. Lee, E.A. Ashley, J. Homburger, et al., Incident atrial fibrillation is associated with MYH7 sarcomeric gene variation in hypertrophic cardiomyopathy, Circ Heart Fail 11 (2018) e005191.
[27] Y. Gao, L. Peng, C. Zhao, MYH7 in cardiomyopathy and skeletal muscle myopathy, Mol. Cell. Biochem. 479 (2024) 393–417.
[28] L.R. Lopes, D. Brito, A. Belo, N. Cardim, Genetic characterization and genotype-phenotype associations in a large cohort of patients with hypertrophic cardiomyopathy - an ancillary study of the Portuguese registry of hypertrophic cardiomyopathy, Int. J. Cardiol. 278 (2019) 173–179.
[29] A.S. Helms, V.T. Tang, T.S. O'Leary, et al., Effects of MYBPC3 loss-of-function mutations preceding hypertrophic cardiomyopathy, JCI Insight 5 (2020).
[30] V. Höller, H. Seebacher, D. Zach, et al., Myocardial deformation analysis in MYBPC3 and MYH7 related sarcomeric hypertrophic cardiomyopathy-the Graz hypertrophic cardiomyopathy registry, Genes 12 (2021).
[31] E.R. Witjas-Paalberends, A. Güçlü, T. Germans, et al., Gene-specific increase in the energetic cost of contraction in hypertrophic cardiomyopathy caused by thick filament mutations, Cardiovasc. Res. 103 (2014) 248–257.

[32] J.G. Seidman, C. Seidman, The genetic basis for cardiomyopathy: from mutation identification to mechanistic paradigms, Cell 104 (2001) 557–567.
[33] D.H. Kim, M.D. Handschumacher, R.A. Levine, et al., In vivo measurement of mitral leaflet surface area and subvalvular geometry in patients with asymmetrical septal hypertrophy: insights into the mechanism of outflow tract obstruction, Circulation 122 (2010) 1298–1307.
[34] H.G. Klues, B.J. Maron, A.L. Dollar, W.C. Roberts, Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy, Circulation 85 (1992) 1651–1660.
[35] M.K. Rausch, F.A. Tibayan, D.C. Miller, E. Kuhl, Evidence of adaptive mitral leaflet growth, J. Mech. Behav. Biomed. Mater. 15 (2012) 208–217.
[36] R.A. Levine, G.J. Vlahakes, X. Lefebvre, et al., Papillary muscle displacement causes systolic anterior motion of the mitral valve. Experimental validation and insights into the mechanism of subaortic obstruction, Circulation 91 (1995) 1189–1195.
[37] M.V. Sherrid, F.A. Chaudhry, D.G. Swistel, Obstructive hypertrophic cardiomyopathy: echocardiography, pathophysiology, and the continuing evolution of surgery for obstruction, Ann. Thorac. Surg. 75 (2003) 620–632.
[38] A.J. Marian, E. Braunwald, Hypertrophic cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy, Circ. Res. 121 (2017) 749–770.
[39] S.K. Balaram, L. Tyrie, M.V. Sherrid, et al., Resection-plication-release for hypertrophic cardiomyopathy: clinical and echocardiographic follow-up, Ann. Thorac. Surg. 86 (2008) 1539–1544, discussion 1544-1535.
[40] C. van der Lee, M.J. Kofflard, L.A. van Herwerden, et al., Sustained improvement after combined anterior mitral leaflet extension and myectomy in hypertrophic obstructive cardiomyopathy, Circulation 108 (2003) 2088–2092.