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Recent Advances in Hypertrophic Cardiomyopathy: A System Review

Yamin Liu, Zhao Li, Xiaofan Guo, Xiong Jing,
Xueli Zhang, Hua Shao, Yufan Guan and
Maria R. Abraham

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Abstract

Hypertrophic cardiomyopathy (HCM) is a common genetic cardiovascular disease present in 1 in 500 of the general population, leading to the most frequent cause of sudden death in young people (including trained athletes), heart failure, and stroke. HCM is an autosomal dominant inheritance, which is associated with a large number of mutations in genes encoding proteins of the cardiac sarcomere. Over the last 20 years, the recognition, diagnosis, and treatment of HCM have been improved dramatically. And moreover, recent advancement in genomic medicine, the growing amount of data from genotype-phenotype correlation studies, and new pathways for HCM help the progress in understanding the diagnosis, mechanism, and treatment of HCM. In this chapter, we aim to outline the symptoms, complications, and diagnosis of HCM; update pathogenic variants (including miRNAs); review the treatment of HCM; and discuss current treatment and efforts to study HCM using induced pluripotent stem cell-derived cardiomyocytes and gene editing technologies. The authors ultimately hope that this chapter will stimulate further research, drive novel discoveries, and contribute to the precision medicine in diagnosis and therapy for HCM.

Keywords: cardiac sarcomere, gene, hypertrophic cardiomyopathy, microRNA, pharmacology

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a heterogeneous cardiac disease with a diverse clinical presentation and course, presenting in all age groups from infancy to the very elderly,

which was first described in 1868, its functional consequences in 1957, left ventricular (LV) asymmetric and especially septal hypertrophy in 1958, and its familial nature in 1960 [1, 2]. HCM is a global disease, affecting 1 in every 500 people [3]. And, the existing epidemiological studies might have underestimated the prevalence of HCM because majority of the original prevalence studies enrolled unrelated adults only and employed a diagnostic criterion of maximal wall thickness (MWT) ≥ 15 mm, or both, thereby resulting in under-recognition of early, familial disease [1, 4]. Enhanced recognition of HCM is important, allowing more timely diagnosis and the implementation of appropriate treatment options for many patients.

HCM is characterized by left ventricular hypertrophy with histological features of myocyte hypertrophy, myofibrillar disarray, and interstitial fibrosis [5]. The thickened and stiff ventricle reduces the compliance of the heart muscle, decreases preload, and leads to the most frequent cause of sudden death in young people (including trained athletes), heart failure, and stroke [6].

Since its first description in the 1950s, much progress has been made in elucidating the extremely heterogeneous genetic, morphogenic, diagnosis, and patient management. The goals of this chapter are to outline the symptoms, complication, and diagnosis of HCM; update published pathogenic variants; and discuss current treatment and efforts to study HCM by using induced pluripotent stem cell-derived cardiomyocytes, next-generation sequencing, and gene editing technologies.

2. Symptoms and complications

HCM is a common inherited cardiomyopathy with a diverse clinical presentation. Most patients with HCM are asymptomatic and have a normal life span but some develop symptoms. The most frequent symptoms of HCM included chest pain, dizziness, shortness of breath, palpitations, fatigue, and inability to perform vigorous exercise. Another devastating manifestation of HCM is sudden cardiac death (SCD) [7].

Furthermore, HCM is related with disease complications that may be profound, with the potential to result in disease progression or premature death [8, 9]. Atrial fibrillation (AF) is the most common sustained arrhythmia in HCM. Paroxysmal episodes or chronic AF ultimately occur in 20–25% of HCM patients, increase in incidence with age, and are linked to left atrial enlargement [10]. AF is a precursor of stroke (incidence, about 1% annually; prevalence, 6%), which is associated with death as well as disability most frequently in the elderly, and progressive heart failure, particularly for patients who have AF before 50 years old and accompanied basal outflow obstruction [11, 12].

Heart failure is another severe complication of HCM. Symptoms of chronic heart failure are frequent; however, the clinical profile of advanced heart failure varies between patients. In some, the thickened and stiff ventricle reduces the compliance of the heart muscle, decreases preload, and contributes to diastolic heart failure [6]. On the other end of the spectrum, typical DCM cases show chamber volume dilatation and thin walls, which reduces contractile force and causes systolic heart failure [13].

Myocardial ischemia: the other common pathologic features of HCM are the thickened and narrowed intramural coronary arteries and myocardial fibrosis by increased collagen deposition, leading to symptoms related to myocardial ischemia [14].

3. Diagnosis

Accurate diagnosis is vital for the management of HCM patients. Echocardiography is the primary method of diagnosis of HCM by determination of left ventricular hypertrophy (LVH) [15], left ventricular outflow tract gradients [16], systolic and diastolic function, as well as mitral valve anatomy and function. Cardiac magnetic resonance imaging (MRI) is becoming more widely used in diagnosis of HCM by determining the extent and location of LVH and the anatomic abnormalities of the mitral valve and papillary muscles [17]. Besides, genetic testing that is now commercially available is currently used most effectively in the identification of affected relatives in families known to have HCM.

3.1. Echocardiography

Echocardiography (echo) was first used to aid diagnosis in HCM in 1969 [18]. Forty years later, echo is central to diagnosis and monitoring of HCM. Diagnostic criteria of HCM by echo: in an adult, HCM is defined by a wall thickness ≥ 15 mm in one or more LV myocardial segments. However, in some cases, genetic and nongenetic disorders may present with a lesser degrees of wall thickening (13–14 mm); for these patients, the diagnosis of HCM requires evaluation of other factors including electrocardiogram (ECG) abnormalities, laboratory tests, and MRI, as well as family history [19]. For children, HCM diagnosis requires an LV wall thickness more than two standard deviations greater than the predicted mean (z-score > 2 , where a z-score is defined as the number of standard deviations from the population mean) [19, 20].

HCM typically can be classified in three categories (**Table 1**), “nonobstructive,” “labile,” or “obstructive at rest” depending on their degree of left ventricular outflow tract obstruction (LVOTO), which result from a hypertrophied interventricular septum and/or abnormal mitral valve morphology. About one-third of patients will have obstruction at rest (peak gradient > 30 mm Hg), and one-third will have labile obstruction (peak gradient > 30 mm Hg only

Hemodynamic state	Conditions	Outflow gradients*
No obstruction	Rest	< 30 mm Hg
	Physiologically provoked	< 30 mm Hg
Labile obstruction	Rest	< 30 mm Hg
	Physiologically provoked	≥ 30 mm Hg
Basal obstruction	Rest	≥ 30 mm Hg

*Gradients are the peak instantaneous continuous wave Doppler gradient.

Table 1. Definition of dynamic left ventricular outflow tract obstruction [2].

during provocation, which includes the Valsalva maneuver, administration of a potent inhaled vasodilator, such as amyl nitrite, and exercise treadmill testing [7]. Another one-third will have no obstruction under provocation or resting conditions (peak gradient <30 mm Hg). It is clinically important to distinguish between the obstructive and nonobstructive forms of HCM because management strategies are largely dependent on the presence or absence of symptoms caused by obstruction.

3.2. Cardiovascular magnetic resonance

Magnetic resonance imaging (MRI) and computed tomography imaging are being used increasingly to evaluate patients with HCM. Cardiovascular magnetic resonance (CMR), with its superior spatial resolution as well as tomographic imaging capability, has provided the opportunity to more accurately characterize the diverse phenotypic expression of HCM [21]. CMR is mainly used in the following situations: (1) the patients are suspected with HCM, but the echocardiogram is inconclusive, mostly because of suboptimal imaging from poor acoustic windows or when hypertrophy is localized to regions of the LV myocardium not well visualized by echocardiography [22]. (2) Hypertrophy confined to the apex (i.e., apical HCM) may be difficult to visualize with echocardiography but is evident with CMR [23]. (3) CMR can more readily detect the presence of apical aneurysms, which are potential implications for management with ICDs and/or anticoagulation; then CMR may identify high-risk status on the basis of massive hypertrophy [24].

4. Hypertrophic cardiomyopathy-associated genes

Hypertrophic cardiomyopathy is a common genetic cardiovascular disease. Genetic disorders account for 60–70% of HCM etiology. Since the identification of the first locus for familial HCM and the first mutation in MYH7-encoded beta-myosin heavy chain 20 years ago [25], over 1500 causal mutations associated with HCM encode sarcomeric proteins have been revealed [26]. According to gene susceptibility, HCM can be divided to “myofilament (sarcomeric) HCM,” “Z-disk HCM,” and “calcium-handling HCM,” with “myofilament (sarcomeric) HCM” being the most common genetic form of HCM, account for 50% of all HCM cases [13]. Recently, large genotype-phenotype analysis correlation studies established implications for septal morphology, disease onset, and prognosis of certain sarcomeric genes, which may further facilitate commercialized genetic testing. On the other hand, unexplained left ventricular hypertrophies that mimic HCM appear in some syndromic diseases. These diseases are usually called phenocopies and may contain rare variants in metabolism genes. These mutations alter myocardial metabolism, resulting in increased wall thickness, cardiac storage abnormalities, and conduction irregularities second to multiple systematic disorders. The information of HCM susceptibility genes and HCM phenocopies are listed in **Tables 2** and **3** [13, 27, 28].

Although more than 1500 mutations linked to hypertrophic cardiomyopathy, most of which are unique to individual families and less evident for pathogenicity. There are four sarcomeric

Gene	Chromosomal position ^a	Protein	HCM-associated mutations	Location or function ^b
<i>ACTA1</i>	1q42.13–q42.2	Actin, alpha 1	1	Sarcomere, skeletal muscle
<i>ACTC1</i>	15q11–q14	Actin, alpha, cardiac muscle 1	25	Actin, alpha, cardiac muscle 1
<i>ACTN2</i>	1q42–q43	Actinin, alpha 2	5	Z-disk
<i>ANKRD1</i>	10q23.33	Ankyrin repeat domain 1	3	Z-disk and nucleus (transcription factor)
<i>BRAF</i>	7q34	v-Raf murine sarcoma viral oncogene homolog B1	1	
<i>COA5</i>	2q11.2	Cytochrome c oxidase assembly factor 5	1	Mitochondrial
<i>CALM3</i>	19q13.2–q13.3	Calmodulin 3 (phosphorylase kinase, delta)	1	Calcium sensor and signal transducer
<i>CALR3</i>	19p13.11	Calreticulin 3	2	endoplasmic reticulum chaperone
<i>CASQ2</i>	1p13.3–p11	Calsequestrin 2	1	Sarcoplasmic reticulum; calcium storage
<i>CASQ2</i>	1p13.3–p11	Calsequestrin 2	1	Sarcoplasmic reticulum; calcium storage
<i>CAV3</i>	3p25	Caveolin 3	1	Plasma membrane
<i>COX15</i>	10q24	Cytochrome c oxidase assembly homolog 15	2	Mitochondrial respiratory chain
<i>CSRP3</i>	11p15.1	Cysteine and glycine-rich protein 3	15	Z-disk
<i>DES</i>	2q35	Desmin	1	Intermediate filament
<i>FHL1</i>	Xq26	Four and a half LIM domains 1	3	Biomechanical stress sensor
<i>FHOD3</i>	18q12	Formin homology 2 domain containing 3	1	Actin-organizing protein
<i>FXN</i>	9q13–q21.1	Frataxin	1	Mitochondrial iron transport and respiration
<i>GLA</i>	Xq22	Galactosidase, alpha	765	Lysosome
<i>JPH2</i>	20q13.12	Junctophilin 2	6	Junctional membrane complexes; calcium signaling
<i>KLF10</i>	8q22.2	Kruppel-like factor 10	6	Transcriptional repressor; inhibits cell growth
<i>MAP2K1</i>	15q22.1–q22.33	Mitogen-activated protein kinase kinase 1	1	MAP kinase kinase; signal transduction
<i>MAP2K2</i>	19p13.3	Mitogen-activated protein kinase kinase 2	1	MAP kinase kinase; signal transduction
<i>MRPL3</i>	3q21–q23	Mitochondrial ribosomal protein L3	1	Mitochondrial ribosomal protein

Gene	Chromosomal position ^a	Protein	HCM-associated mutations	Location or function ^b
<i>MTOT1</i>	6q13	Mitochondrial tRNA translation optimization 1	2	Mitochondrial tRNA modification
<i>MYBPC3</i>	11p11.2	Myosin-binding protein C, cardiac	506	Sarcomere
<i>MYH6</i>	14q12	Alpha-myosin heavy chain	3	Sarcomere
<i>MYH7</i>	14q12	Beta-myosin heavy chain	491	Sarcomere
<i>MYL2</i>	12q23–q24.3	ventricular myosin regulatory light chain	20	Sarcomere
<i>MYL3</i>	3p21.3–p21.2	Myosin light chain 3	16	Sarcomere
<i>MYLK2</i>	20q13.31	Myosin light chain kinase 2	2	Calcium/calmodulin-dependent kinase
<i>MYO6</i>	6q13	Myosin VI	1	Actin-based reverse-direction motor protein
<i>MYOM1</i>	18p11.31	Myomesin 1	1	Sarcomere
<i>MYOZ2</i>	4q26–q27	Myozenin 2	2	Z-disk
<i>MYPN</i>	10q21.3	Myopalladin	8	Z-disk
<i>NDUFAF1</i>	15q11.2–q21.3	NADH dehydrogenase (ubiquinone) complex I, assembly factor 1	2	Mitochondrial chaperone
<i>NDUFV2</i>	18p11.31–p11.2	NADH dehydrogenase (ubiquinone) avoprotein 2	1	Mitochondrial respiratory chain
<i>NEXN</i>	1p31.1	Nexilin	2	Z-disk
<i>OBSCN</i>	1q42.13	Obscurin	1	Sarcomere
<i>PDLIM3</i>	4q35	PDZ and LIM domain 3	1	Z-disk
<i>PRKAG2</i>	7q36.1	5'-AMP-activated protein kinase subunit gamma-2	7	energy sensor protein kinase
<i>PLN</i>	6q22.1	Phospholamban	7	Sarcoplasmic reticulum; regulates Ca ²⁺ -ATPase
<i>RAF1</i>	3p25	v-Raf-1 murine leukemia viral oncogene homolog 1	1	Serine/threonine-protein kinase; signal transduction
<i>SLC25A3</i>	12q23	Solute carrier family 25, member 3	1	Phosphate carrier protein (cytosol to mitochondria)
<i>SLC25A4</i>	4q35	Solute carrier family 25, member 4	2	Adenine nucleotide translocator (cytosol/mitochondria)
<i>SOS1</i>	2p22–p21	Son of sevenless homolog 1	1	Guanine nucleotide exchange factor for RAS proteins; signal transduction
<i>SRI</i>	7q21.1	Sorcin	2	Calcium-binding; modulates

Gene	Chromosomal position ^a	Protein	HCM-associated mutations	Location or function ^b
<i>TCAP</i>	17q12	Telethonin	7	Z-disk
<i>TNNC1</i>	3p21.3–p14.3	Troponin C	14	Sarcomere
<i>TNNI3</i>	19q13.4	Troponin I	70	Sarcomere
<i>TNNT2</i>	1q32	Troponin T	90	Sarcomere
<i>TPM1</i>	15q22.1	Alpha-tropomyosin	38	Sarcomere
<i>TRIM63</i>	1p34–p33	Tripartite motif-containing 63	3	Sarcomere; regulates protein degradation
<i>TTN</i>	2q31	Titin	6	Sarcomere
<i>VCL</i>	10q22.1–q23	Vinculin	1	Sarcomere

^aHuman genome mutation database (<http://www.hgmd.cf.ac.uk/ac/index.php>).

^bNational Center for Biotechnology information (<http://ncbi.nlm.nih.gov/>). Abbreviations: HCM, hypertrophic cardiomyopathy; tRNA, transfer RNA; AMP, adenosine monophosphate; ATP, adenosine triphosphate.

Table 2. HCM susceptibility genes [28].

Gene	Locus	Protein	Syndrome
TAZ	Xq28	Tafazzin (G4.5)	Barth syndrome/LVNC
DTNA	18q12	Alpha-dystrobrevin	Barth syndrome/LVNC
PRKAG2	7q35–q36.36	AMP-activated protein kinase	WPW/HCM
LAMP2	Xq24	Lysosome-associated membrane protein 2	Danon's syndrome/WPW
GAA	17q25.2–q25.3	Alpha-1,4-glucosidase deficiency	Pompe's disease
GLA	Xq22	Alpha-galactosidase A	Fabry's disease
AGL	1p21	Amylo-1,6-glucosidase	Forbes disease
FXN	9q13	Frataxin	Friedrich's ataxia
PTPN11	12q24.1	Protein tyrosine phosphatase, nonreceptor type 11, SHP-2	Noonan's syndrome, LEOPARD syndrome
RAF1	3p25	V-RAF-1 murine leukemia viral oncogene homolog 1	Noonan's syndrome, LEOPARD syndrome
KRAS	12p12.1	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	Noonan's syndrome
SOS1	2p22–p21	Son of sevenless homolog 1	Noonan's syndrome

AMP, adenosine monophosphate; HCM, hypertrophic cardiomyopathy; LEOPARD, mnemonic for syndrome with clinical characteristics of lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary hypertension, abnormal genitalia, retarded growth, deafness; LVNC, left ventricular noncompaction; WPW, Wolff-Parkinson-White syndrome

Table 3. HCM phenocopies [29].

genes that carry the majority of HCM-related mutations and encode the proteins: myosin heavy chain (*MYH7*) and myosin-binding protein C3 (*MYBPC3*) are most common, together account for 75–80% of sarcomere mutations in HCM, while an additional 10% come from cardiac troponin T type 2 (*TNNT2*) and cardiac troponin I type 3 (*TNNI3*) (**Figure 1**) [3].

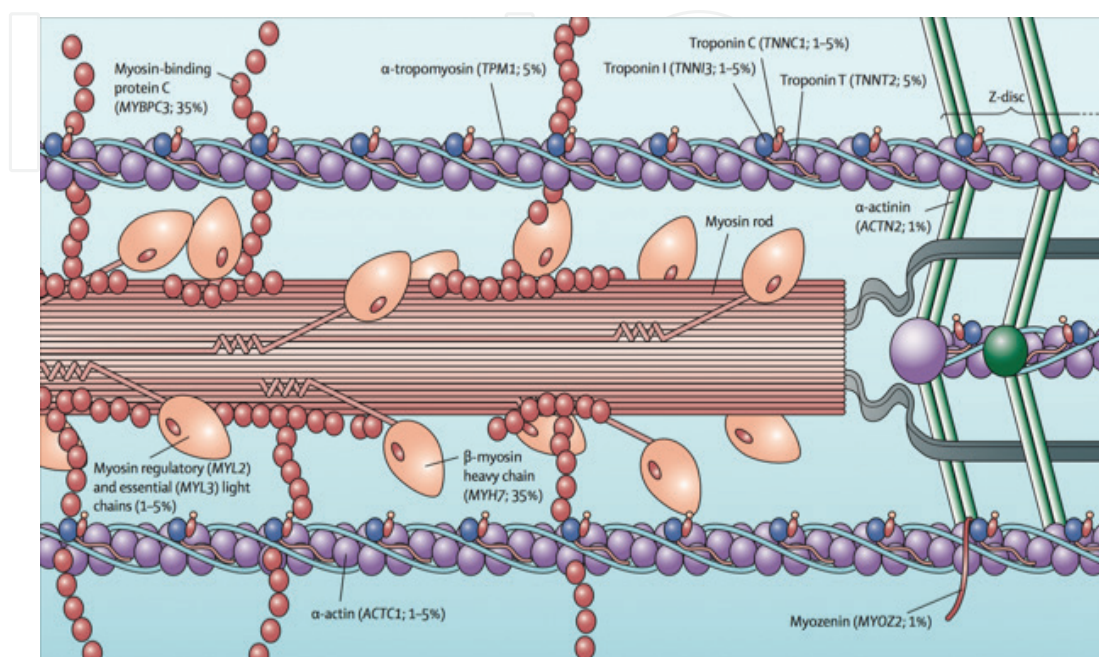


Figure 1. Locations of genes within the cardiac sarcomere known to cause hypertrophic cardiomyopathy [3].

5. Hypertrophic cardiomyopathy-associated miRNA

Despite extensive exploration of many genes, potential genetic associations remain to be found in approximately 30% of HCM patients. The recent newly developed field that has won extensive attention is microRNAs (miRNAs) in cardiovascular biology. miRNAs are noncoding RNAs with a length of approximately 22 ribonucleic acid molecules that bind mRNAs and regulate their expression through posttranslational repression or mRNA cleavage and degradation [30, 31]. It is estimated that the human genome contains more than 1000 miRNAs, which regulate at least 30–60% of protein-coding genes [32]. Multiple studies revealed that single or combined function of miRNAs is directly involved in the pathophysiology of cardiac hypertrophy, fibrosis, and electrical remodeling in vivo and in vitro [33]. The biological functions regulated by miRNAs affecting HCM are listed below (**Table 4** and **Figure 2**). Since miRNAs play a more and more important role in the development of HCM, they are being studied for potential diagnostic biomarkers and a promising therapeutics for HCM.

The schematic shows the miRNAs and their targets involving in cellular hypertrophy, gene switching, electrical remodeling, as well as fibrosis during cardiac hypertrophy. An upward

miRNA	Target	Biological effect	References
miR-340	Dystrophin	Cardiac eccentric Cardiac hypertrophy Heart failure	[34]
miR-133	RhoA Cdc42 Nelf-A/WHSC2 HCN2	Cardiac hypertrophy Heart failure	[35, 36]
miR-1	IGF-1 calmodulin Mef2a RasGAP Cdk-9	Cardiac hypertrophy Dilated cardiomyopathies Heart failure	[35, 37, 38]
miR-208	Thrap1 Myostatin	Cardiac hypertrophy	[39]
miR-21	sprouty1	Cardiac hypertrophy Cardiac fibrosis	[40]
miR-23a	MuRF1	Cardiac hypertrophy	[41]
miR-195		Cardiac hypertrophy Heart failure	[42]
miR-99a	mTOR FGFR3	Cardiac hypertrophy Heart failure	[43]
miR-199a	NFAT	Cardiac hypertrophy Cardiac fibrosis Heart failure	[44]
miR-30	CTGF	Cardiac fibrosis	[35]
miR-29		Cardiac hypertrophy Cardiac fibrosis	[45]

Thrap1, thyroid hormone receptor-associated protein 1; MuRF1, myostatin, muscle-specific ring finger protein 1; RasGAP, Ras GTPase-activating protein; Cdk9, cyclin-dependent kinase 9; Mef2a, calmodulin, myocyte enhancer factor 2A; IGF1, insulin-like growth factor 1; CTGF, connective tissue growth factor; HCN2, hyperpolarization-activated, cyclic nucleotide-gated K⁺ p 2; FGFR3, fibroblast growth factor receptor 3; NFAT, nuclear factor of activated T-cells

Table 4. MiRNA in cardiac hypertrophy.

or a downward arrow is used to represent the upregulation or downregulation of a specific miRNA, respectively. All listed targets have been validated: Thrap1, thyroid hormone receptor-associated protein 1; MuRF1, myostatin, muscle-specific ring finger protein 1; RasGAP, Ras

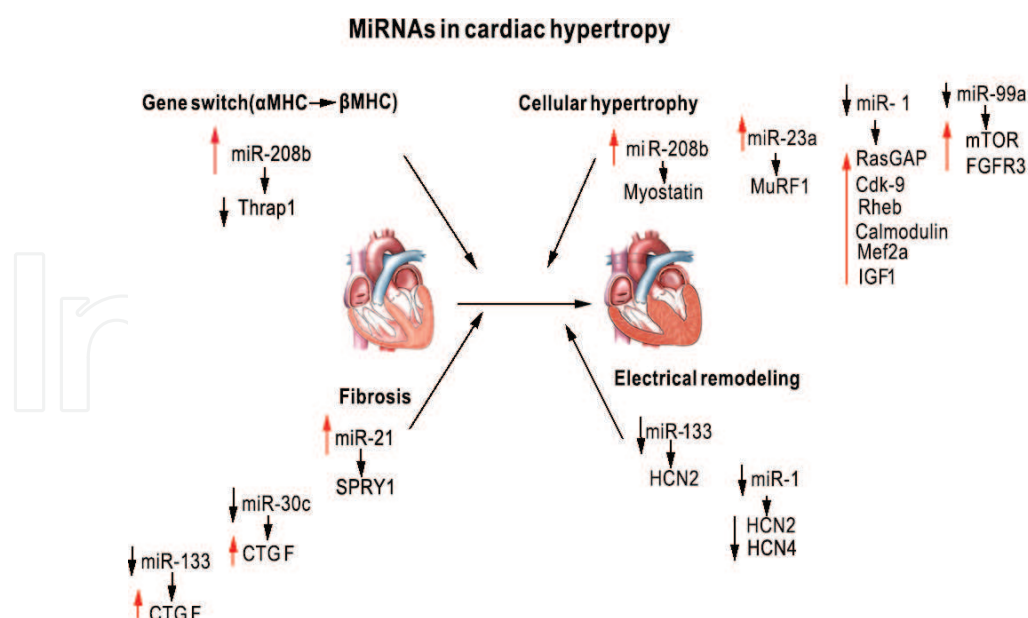


Figure 2. MiRNAs in hypertrophic cardiomyopathy.

GTPase-activating protein; Cdk9, cyclin-dependent kinase 9; Rheb, Ras homolog enriched in the brain; Mef2a, calmodulin, myocyte enhancer factor 2A; IGF1, insulin-like growth factor 1; SPRY1, sprouty 1; CTGF, connective tissue growth factor; HCN2/4, hyperpolarization-activated, cyclic nucleotide-gated K⁺ p 2/4; and FGFR3, fibroblast growth factor receptor 3.

6. Treatment of HCM

As is typical for many forms of CVD, many current therapeutic strategies for HCM try to alleviate symptoms and prevent complications. Although once considered rare and terminal with annual mortality rates of up to 6%, HCM has now emerged as a very treatable form of heart disease [46]. Due to contemporary management strategies and treatment interventions, including ICDs for SD prevention, a variety of available surgical HCM mortality rates have dropped to 0.5% per year [47].

6.1. Pharmacology management

It has been clearly demonstrated that left ventricular outflow tract obstruction at rest in HCM patients is a strong, independent predictor of progression to severe symptoms of heart failure and of death [48]. Considering the mechanisms underlying myocardial contraction (calcium ions binding to troponin C and excitation-contraction coupling), a number of medical regimens have been used in these patients with the goal of lessening or eliminating the LVOT gradient through negative inotropy [7].

Pharmacological therapy of HCM consists of β -blockers and calcium channel blockers. β -Blockers and calcium channel blockers are used to improve diastolic function in patients

with HCM. Small and mostly retrospective studies suggest that oral propranolol can abolish or reduce resting and provokable LVOTO and provide symptomatic benefit [49, 50]. Donald et al.'s study showed that β -blocker abolished the increase in gradient caused by isoproterenol and, more importantly, halved the increase in gradient caused by exercise [51]. In a 5-year follow-up, a study demonstrated that propranolol significantly improved the HCM patient's syndrome (dyspnea, angina, palpitations, dizziness, and syncope) by 58–100% [52].

Calcium channel blockade is used to HCM patients since it might ameliorate the hypercontractility characteristic of HCM. Verapamil, which has the best profile of the calcium antagonists, has been widely used in the treatment of HCM. A double-blind, placebo-controlled crossover trial studied oral propranolol, verapamil, and placebo, to 19 patients with HCM (17 with hypertrophic obstructive cardiomyopathy). Most patients derived symptomatic benefit from drug therapy, especially with verapamil [53]. In a recent study, the calcium channel blocker diltiazem was used to treat 38 HCM patients carrying *MYBPC3* mutation; results showed that diltiazem is safe and may improve early LV remodeling in HCM [54].

Another medicine used in hypertrophic obstructive cardiomyopathy (HOCM) patients is disopyramide, which is an effective negative inotropic agent by mediating sodium-calcium exchange [55]. Pollick et al. administered intravenous disopyramide to 43 patients with HOCM. The LVOT gradient was abolished or reduced; the effect was greater than that seen previously for either propranolol or verapamil [56]. By virtue of its atrial antiarrhythmic properties, disopyramide may be of particular benefit in HOCM patients with atrial fibrillation. Then, the ESC guideline recommended disopyramide, as Class IA anti-arrhythmic drug, which may be added to a maximum tolerated dose (usually 400–600 mg/day), if β -blockers alone are ineffective [19]. It can improve exercise tolerance and functional capacity as well as abolish basal LV outflow pressure gradients without proarrhythmic effects or an increased risk of sudden cardiac death.

6.2. Invasive treatment of LVOTO

Invasive treatment should be considered in patients with an LVOTO. The American and European colleges of cardiology recommend invasive treatment to (1) patients with labile obstruction and peak LVOT pressure gradients ≥ 50 mm Hg during exercise or provocation and resting gradients >30 mm Hg and (2) patients with moderate-to-severe symptoms (New York Heart Association (NYHA) functional classes III–IV) refractory to medical therapy [7, 19]. Two common surgical procedures performed in about 3% of obstructive HCM patients are septal myectomy and alcohol septal ablation [28].

6.2.1. Ventricular septal myectomy

Since the time of the first myectomy through the aortic root by Cleland in Great Britain in November 1958 [57], ventricular septal myectomy (Morrow procedure) is the most commonly performed surgical procedure used to treat LVOTO [58]. In a 10-year follow-up in 185 patients, the patients with hypertrophic cardiomyopathy (HCM) were treated with septal myotomy-myomectomy (MM) with a significant reduction in left ventricular outflow gradient at rest,

which improves exercise capacity and symptoms. Long-term symptomatic benefit is achieved in 70–80% of patients with a long-term survival compared to that of the general population [59]. Notably, operative mortality at surgical centers is now low, reduced to less than 1%.

6.2.2. Alcohol septal ablation

Percutaneous alcohol septal ablation is an alternative to surgical myectomy, which is a selective injection of alcohol into a septal perforator artery to create a localized septal scar. There are no randomized trials comparing surgery and septal alcohol ablation (SAA), but several meta-analyses have shown that SAA procedures improve functional status with a similar surgery in terms of gradient reduction, symptom improvement, and exercise capacity [60]. The main nonfatal complications are AV block in 7–20% of patients and a procedural mortality of about 2% [3]. Alcohol ablation has been recommended as a selective alternative for older patients, those with comorbidities, or patients with an absolute reluctance toward surgery.

6.2.3. Implant cardiac defibrillator

In addition to myectomy, the implantable cardioverter-defibrillator (ICD) has proven to be effective in terminating life-threatening ventricular tachyarrhythmia in HCM, altering the natural course of the disease and prolonging life [61, 62]. The indications for ICD placement are (1) positive family history of several sudden cardiac deaths in a distant family member, (2) nonsustained ventricular tachycardia on Holter monitoring, (3) LVH >30 mm, (4) prior unexplained syncope during exercise or at rest, and (5) an abnormal blood pressure response during exercise, which can be described as progressive decrease in the systolic value by 20 mm Hg after an initial increase or an increase in systolic blood pressure of <20 mm Hg from the baseline value or a [2, 63, 64]. The decision for placement of primary prevention of ICD in HCM often involves a large measure of individual clinical judgment, particularly when the evidence for risk is ambiguous.

7. Recent advances toward precision medicine for HCM

7.1. iPSC-CMs

Induced pluripotent stem cells (also known as iPS cells or iPSCs) are a type of embryonic stemlike cells that can be generated directly from adult cells [65–67]. The emergence of patient-derived induced pluripotent stem cells (iPSCs), which can be differentiated into functional cardiomyocytes (CMs) in vitro, may provide an exciting new approach to understand disease mechanisms underpinning inherited heart diseases (**Figure 3**) [26, 68].

iPSC-CMs derived from a patient with HCM caused by the MYH7 mutation p.Arg442Gly and mutation p.Arg663His have demonstrated the pathogenic effects [69, 70]. HCM iPSC-CMs exhibited structural abnormalities consistent with the HCM phenotype. Similar calcium-handling abnormalities were identified, consistent with observations made from animal models [70]. These studies explored the possible patient-specific and mutation-specific disease mechanism of HCM and demonstrated the potential of using HCM iPSC-CMs for future development of therapeutic strategies.

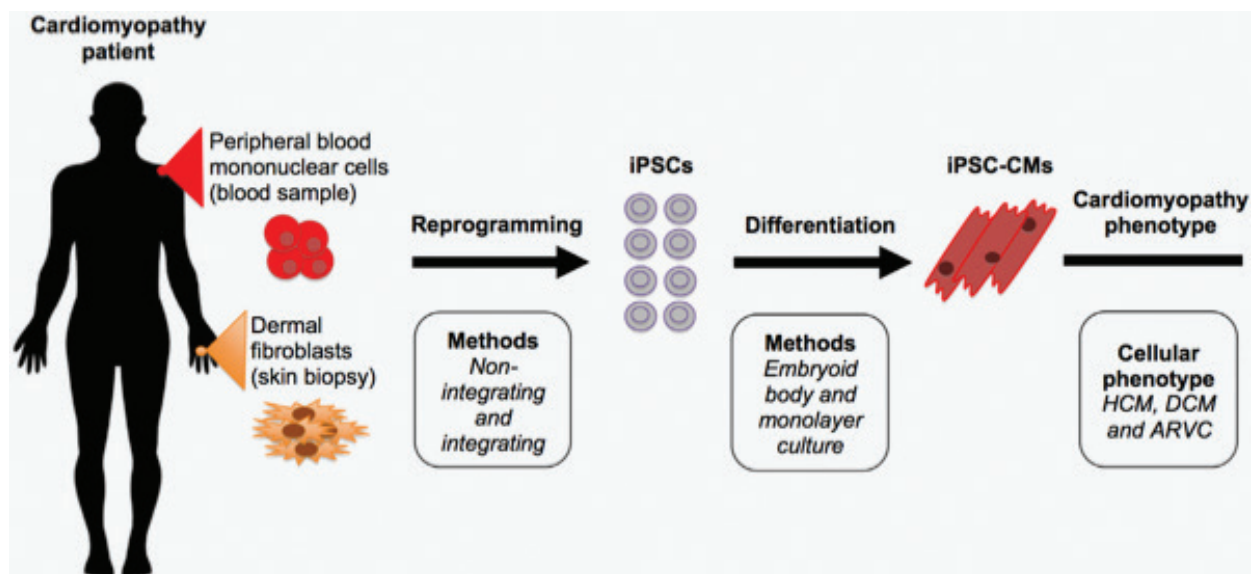


Figure 3. Generation of iPSCs from patients and then the differentiation to cardiomyocytes and then to their use in different cardiomyopathies. HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy.

In vivo direct cardiac reprogramming of somatic cells into cardiomyocytes is a potential offshoot of current reprogramming techniques but has not yet been tested in humans [71]. For HCM in particular, the possibility of converting cardiac fibroblasts into functional cardiomyocytes could theoretically ameliorate hypertrophy and improve diastolic function.

Although still in a nascent stage, direct cardiac reprogramming has undergone great advances and attracted considerable attention, these techniques could offer a renewable source of cardiomyocytes and deliver medicine individually tailored to each patient [72].

7.2. Gene editing technology

Gene editing is rapidly progressing from being a research/screening tool to one that promises important applications downstream in drug development and cell therapy. As primarily inherited cardiomyopathies, HCM is perhaps the strongest candidate for gene editing technologies [73, 74]. Recently, genome modification technologies, such as TALEN (transcription activator-like effector nucleases), ZFN (zinc finger nucleases), as well as CRISPR/Cas9 nuclease (clustered regularly interspaced short palindromic repeats/Cas9 nuclease systems), allow for specific editing of individual gene mutations [74, 75].

This CRISPR/Cas9 system makes it possible to efficiently, easily, and cheaply modify the genome, which is the current front-runner of these gene modification technologies [76]. To date, the CRISPR/Cas9 system has been used to successfully engineer cardiomyopathy into zebra fish and mice models and is currently being applied to larger animals such as pigs and nonhuman primates [77]. This new technology promises to provide researchers with more accurate model for studying and treating HCM [78].

8. Conclusion

Hypertrophic cardiomyopathy (HCM) is a global and is considered one of the most common genetic cardiovascular diseases. Genetic variants, molecular mechanisms, and clinical phenotypes of HCM vary on a patient-by-patient basis. Fifty years ago, HCM was thought to be an obscure disease. Today, however, our understanding and ability to diagnose patients with HCM have improved dramatically, due to improvements in screening and detection of gene defects in the human genome as well as iPSC-CM model in HCM patients and gene editing technology (including CRISPR/Cas9). However, currently, treatments for HCM are directed at symptomatic relief, preventing sudden death. The future goal of research is focused on changing the natural course of the disease and preventing its phenotypic expression. Working group from clinical, translational, and basic science aspects should work together to develop novel treatments to HCM. Then, finally, with the effort of all groups, we will reach the goal of the precision medicine of HCM.

Author details

Yamin Liu^{1,2*}, Zhao Li³, Xiaofan Guo³, Xiong Jing⁴, Xueli Zhang¹, Hua Shao¹, Yufan Guan² and Maria R. Abraham²

*Address all correspondence to: liuyamincn@hotmail.com

1 Department of Pharmacy, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China

2 Department of Cardiology, School of Medicine, Johns Hopkins University, MD, USA

3 Department of Cardiology, The First Hospital of China Medical University, Shenyang, Liaoning, China

4 Department of Pharmacology, Nanjing Medical University, Nanjing, China

References

- [1] Sen-Chowdhry S, Jacoby D, Moon JC, McKenna WJ. Update on hypertrophic cardiomyopathy and a guide to the guidelines. *Nature. Reviews.* 2016;**13**(11):651-675
- [2] Hensley N, Dietrich J, Nyhan D, Mitter N, Yee MS, Brady M. Hypertrophic cardiomyopathy: A review. *Anesthesia and Analgesia.* 2015;**120**(3):554-569
- [3] Maron BJ, Maron MS. Hypertrophic cardiomyopathy. *Lancet.* 2013;**381**(9862):242-255
- [4] Semsarian C, Ingles J, Maron MS, Maron BJ. New perspectives on the prevalence of hypertrophic cardiomyopathy. *Journal of the American College of Cardiology.* 2015;**65**(12):1249-1254

- [5] Towbin JA. Hypertrophic cardiomyopathy. *Pacing and Clinical Electrophysiology*. 2009; **32**Suppl 2:S23-31
- [6] Jacoby DL, DePasquale EC, McKenna WJ. Hypertrophic cardiomyopathy: diagnosis, risk stratification and treatment. *CMAJ*. 2013;**185**(2):127-134
- [7] American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Society, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, Gersh BJ, 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. *The Journal of Thoracic and Cardiovascular Surgery*. 2011;**142**(6):1303-1338
- [8] Yang YJ, Fan CM, Yuan JQ, Zhang HB, Duan FJ, Wang ZM, Guo XY, Zhai SS, An SY, Hang F et al. Long-term survival after acute myocardial infarction in patients with hypertrophic cardiomyopathy. *Clinical Cardiology*. 2017;**40**(1):26-31
- [9] Rodrigues JC, Rohan S, Ghosh Dastidar A, Harries I, Lawton CB, Ratcliffe LE, Burchell AE, Hart EC, Hamilton MC, Paton JF et al. Hypertensive heart disease versus hypertrophic cardiomyopathy: multi-parametric cardiovascular magnetic resonance discriminators when end-diastolic wall thickness ≥ 15 mm. *European Radiology*. 2017;**27**(3):1125-1135
- [10] Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. *JAMA*. 1999;**281**(7):650-655
- [11] Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA*. 2002;**287**(10):1308-1320
- [12] Maron BJ, Olivotto I, Bellone P, Conte MR, Cecchi F, Flygenring BP, Casey SA, Gohman TE, Bongioanni S, Spirito P. Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. *Journal of the American College of Cardiology*. 2002;**39**(2):301-307
- [13] Kraker J, Viswanathan SK, Knoll R, Sadayappan S. Recent advances in the molecular genetics of familial hypertrophic cardiomyopathy in south Asian descendants. *Frontiers in Physiology*. 2016;**7**:499
- [14] Shirani J, Pick R, Roberts WC, Maron BJ. Morphology and significance of the left ventricular collagen network in young patients with hypertrophic cardiomyopathy and sudden cardiac death. *Journal of the American College of Cardiology*. 2000;**35**(1):36-44
- [15] Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation*. 1977;**55**(4):613-618
- [16] Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvlin JT, Nistri S, Cecchi F, Udelson JE, Maron BJ. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation* 2006;**114**(21):2232-2239

- [17] Heatlie GJ, Pointon K. Cardiac magnetic resonance imaging. *Postgraduate Medical Journal*. 2004;**80**(939):19-22
- [18] Shah PM, Gramiak R, Kramer DH. Ultrasound localization of left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy. *Circulation* 1969;**40**(1):3-11
- [19] Authors/Task Force Members, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, et al. 2014 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). *European Heart Journal*. 2014;**35**(39):2733-2779
- [20] Kampmann C, Wiethoff CM, Wenzel A, Stolz G, Betancor M, Wippermann CF, Huth RG, Habermehl P, Knuf M, Emschermann T, et al. Normal values of M mode echocardiographic measurements of more than 2000 healthy infants and children in central Europe. *Heart (British Cardiac Society)*. 2000;**83**(6):667-672
- [21] Maron MS. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *Journal of Cardiovascular Magnetic Resonance*. 2012;**14**:13
- [22] Maron MS, Maron BJ, Harrigan C, Buross J, Gibson CM, Olivetto I, Biller L, Lesser JR, Udelson JE, Manning WJ, et al. Hypertrophic cardiomyopathy phenotype revisited after 50 years with cardiovascular magnetic resonance. *Journal of the American College of Cardiology*. 2009;**54**(3):220-228
- [23] Moon JC, Fisher NG, McKenna WJ, Pennell DJ. Detection of apical hypertrophic cardiomyopathy by cardiovascular magnetic resonance in patients with non-diagnostic echocardiography. *Heart (British Cardiac Society)*. 2004;**90**(6):645-649
- [24] Maron MS, Lesser JR, Maron BJ. Management implications of massive left ventricular hypertrophy in hypertrophic cardiomyopathy significantly underestimated by echocardiography but identified by cardiovascular magnetic resonance. *The American Journal of Cardiology*. 2010;**105**(12):1842-1843
- [25] Jarcho JA, McKenna W, Pare JA, Solomon SD, Holcombe RF, Dickie S, Levi T, Donis-Keller H, Seidman JG, Seidman CE. Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. *The New England Journal of Medicine*. 1989;**321**(20):1372-1378
- [26] Ross SB, Fraser ST, Semsarian C. Induced pluripotent stem cells in the inherited cardiomyopathies: From disease mechanisms to novel therapies. *Trends in Cardiovascular Medicine*. 2016;**26**(8):663-672
- [27] Landstrom AP, Ackerman MJ. Mutation type is not clinically useful in predicting prognosis in hypertrophic cardiomyopathy. *Circulation*. 2010;**122**(23):2441-2449; discussion 2450
- [28] Roma-Rodrigues C, Fernandes AR. Genetics of hypertrophic cardiomyopathy: Advances and pitfalls in molecular diagnosis and therapy. *The Application of Clinical Genetics*. 2014;**7**:195-208

- [29] Bos JM, Towbin JA, Ackerman MJ. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. *Journal of the American College of Cardiology*. 2009;**54**(3):201-211
- [30] Bartel DP. MicroRNAs: Genomics, biogenesis, mechanism, and function. *Cell*. 2004;**116**(2): 281-297
- [31] Papageorgiou N, Tslamandris S, Giolis A, Tousoulis D: MicroRNAs in Cardiovascular Disease: Perspectives and Reality. *Cardiology in review* 2016;**24**(3):110-118
- [32] Zhao W, Zhao SP, Zhao YH. MicroRNA-143/-145 in cardiovascular diseases. *BioMed Research International*. 2015;**2015**:531740
- [33] Condorelli G, Latronico MV, Cavarretta E. microRNAs in cardiovascular diseases: Current knowledge and the road ahead. *Journal of the American College of Cardiology*. 2014;**63**(21):2177-2187
- [34] Zhou J, Gao J, Zhang X, Liu Y, Gu S, Zhang X, An X, Yan J, Xin Y, Su P. microRNA-340-5p functions downstream of cardiotrophin-1 to regulate cardiac eccentric hypertrophy and heart failure via target gene dystrophin. *International Heart Journal*. 2015;**56**(4):454-458 (electronic)
- [35] Han M, Toli J, Abdellatif M. MicroRNAs in the cardiovascular system. *Current Opinion in Cardiology*. 2011;**26**(3):181-189
- [36] Care A, Catalucci D, Felicetti F, Bonci D, Addario A, Gallo P, Bang ML, Segnalini P, Gu Y, Dalton ND et al. MicroRNA-133 controls cardiac hypertrophy. *Nature Medicine*. 2007;**13**(5):613-618
- [37] Ikeda S, He A, Kong SW, Lu J, Bejar R, Bodyak N, Lee KH, Ma Q, Kang PM, Golub TR et al. MicroRNA-1 negatively regulates expression of the hypertrophy-associated calmodulin and Mef2a genes. *Molecular and Cellular Biology*. 2009;**29**(8):2193-2204
- [38] Elia L, Contu R, Quintavalle M, Varrone F, Chimenti C, Russo MA, Cimino V, De Marinis L, Frustaci A, Catalucci D et al. Reciprocal regulation of microRNA-1 and insulin-like growth factor-1 signal transduction cascade in cardiac and skeletal muscle in physiological and pathological conditions. *Circulation*. 2009;**120**(23):2377-2385
- [39] Callis TE, Pandya K, Seok HY, Tang RH, Tatsuguchi M, Huang ZP, Chen JF, Deng Z, Gunn B, Shumate J, et al. MicroRNA-208a is a regulator of cardiac hypertrophy and conduction in mice. *The Journal of Clinical Investigation*. 2009;**119**(9):2772-2786
- [40] Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, Galuppo P, Just S, Rottbauer W, Frantz S, et al. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. *Nature*. 2008;**456**(7224):980-984
- [41] Sayed D, Hong C, Chen IY, Lypowy J, Abdellatif M. MicroRNAs play an essential role in the development of cardiac hypertrophy. *Circulation Research*. 2007;**100**(3):416-424

- [42] van Rooij E, Sutherland LB, Liu N, Williams AH, McAnally J, Gerard RD, Richardson JA, Olson EN. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;**103**(48):18255-18260
- [43] Li Q, Xie J, Wang B, Li R, Bai J, Ding L, Gu R, Wang L, Xu B. Overexpression of microRNA-99a attenuates cardiac hypertrophy. *PLoS One*. 2016;**11**(2):e0148480
- [44] da Costa Martins PA, Salic K, Gladka MM, Armand AS, Leptidis S, el Azzouzi H, Hansen A, Coenen-de Roo CJ, Bierhuizen MF, van der Nagel R et al. MicroRNA-199b targets the nuclear kinase Dyrk1a in an auto-amplification loop promoting calcineurin/NFAT signalling. *Nature Cell Biology*. 2010;**12**(12):1220-1227
- [45] Roncarati R, Viviani Anselmi C, Losi MA, Papa L, Cavarretta E, Da Costa Martins P, Contaldi C, Sacconi Jotti G, Franzone A, Galastri L, et al. Circulating miR-29a, among other up-regulated microRNAs, is the only biomarker for both hypertrophy and fibrosis in patients with hypertrophic cardiomyopathy. *Journal of the American College of Cardiology*. 2014;**63**(9):920-927 (electronic)
- [46] Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivetto I, Maron MS. Hypertrophic cardiomyopathy: Present and future, with translation into contemporary cardiovascular medicine. *Journal of the American College of Cardiology*. 2014;**64**(1):83-99
- [47] Maron BJ, Rowin EJ, Casey SA, Link MS, Lesser JR, Chan RH, Garberich RF, Udelson JE, Maron MS. Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. *Journal of the American College of Cardiology*. 2015;**65**(18):1915-1928
- [48] Maron MS, Olivetto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *The New England Journal of Medicine*. 2003;**348**(4):295-303
- [49] Adelman AG, Shah PM, Gramiak R, Wigle ED. Long-term propranolol therapy in muscular subaortic stenosis. *British Heart Journal*. 1970;**32**(6):804-811
- [50] Fifer MA, Vlahakes GJ. Management of symptoms in hypertrophic cardiomyopathy. *Circulation*. 2008;**117**(3):429-439
- [51] Harrison DC, Braunwald E, Glick G, Mason DT, Chidsey CA, Ross J, Jr. Effects of beta adrenergic blockade on the circulation with particular reference to observations in patients with hypertrophic subaortic stenosis. *Circulation*. 1964;**29**:84-98
- [52] Frank MJ, Abdulla AM, Canedo MI, Saylors RE. Long-term medical management of hypertrophic obstructive cardiomyopathy. *The American Journal of Cardiology*. 1978;**42**(6):993-1001
- [53] Gilligan DM, Chan WL, Joshi J, Clarke P, Fletcher A, Krikler S, Oakley CM. A double-blind, placebo-controlled crossover trial of nadolol and verapamil in mild and moderately symptomatic hypertrophic cardiomyopathy. *Journal of the American College of Cardiology*. 1993;**21**(7):1672-1679

- [54] Ho CY, Lakdawala NK, Cirino AL, Lipshultz SE, Sparks E, Abbasi SA, Kwong RY, Antman EM, Semsarian C, Gonzalez A et al. Diltiazem treatment for pre-clinical hypertrophic cardiomyopathy sarcomere mutation carriers: a pilot randomized trial to modify disease expression. *JACC: Heart Failure*. 2015;**3**(2):180-188
- [55] Kondo N, Mizukami M, Shibata S. Negative inotropic effects of disopyramide on guinea-pig papillary muscles. *British Journal of Pharmacology*. 1990;**101**(4):789-792
- [56] Pollick C, Kimball B, Henderson M, Wigle ED. Disopyramide in hypertrophic cardiomyopathy. I. Hemodynamic assessment after intravenous administration. *The American Journal of Cardiology*. 1988;**62**(17):1248-1251
- [57] Morrow AG, Brockenbrough EC. Surgical treatment of idiopathic hypertrophic subaortic stenosis: Technic and hemodynamic results of subaortic ventriculomyotomy. *Annals of Surgery*. 1961;**154**:181-189
- [58] Morrow AG, Reitz BA, Epstein SE, Henry WL, Conkle DM, Itscoitz SB, Redwood DR. Operative treatment in hypertrophic subaortic stenosis. Techniques, and the results of pre and postoperative assessments in 83 patients. *Circulation*. 1975;**52**(1):88-102
- [59] Krajcer Z, Leachman RD, Cooley DA, Coronado R. Septal myotomy-myomectomy versus mitral valve replacement in hypertrophic cardiomyopathy. Ten-year follow-up in 185 patients. *Circulation*. 1989;**80**(3 Pt 1):I57-64
- [60] Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. *Lancet*. 1995;**346**(8969):211-214
- [61] Yin K, Ding L, Li Y, Hua W: Long-term follow-up of arrhythmogenic right ventricular cardiomyopathy patients with an implantable cardioverter-defibrillator for prevention of sudden cardiac death. *Clinical cardiology* 2017;**40**(4):216-221
- [62] Amara N, Boveda S, Defaye P, Klug D, Treguer F, Amet D, Perier MC, Gras D, Algalarrondo V, Bouzeman A, et al. Implantable cardioverter-defibrillator therapy among patients with non-ischaemic vs. ischaemic cardiomyopathy for primary prevention of sudden cardiac death. *Europace*; 2017:1-8. Doi: 10.1093/europace/euw379
- [63] Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA*. 2007;**298**(4):405-412
- [64] Jayatilake I, Doolan A, Ingles J, McGuire M, Booth V, Richmond DR, Semsarian C. Long-term follow-up of implantable cardioverter defibrillator therapy for hypertrophic cardiomyopathy. *The American Journal of Cardiology*. 2004;**93**(9):1192-1194
- [65] Quintanilla RH, Jr. Cellular characterization of human pluripotent stem cells. *Methods in Molecular Biology* (Clifton, NJ) 2013;**997**:179-190
- [66] Hackett CH, Fortier LA. Embryonic stem cells and iPS cells: Sources and characteristics. *The Veterinary Clinics of North America. Equine Practice*. 2011;**27**(2):233-242

- [67] Chou SJ, Yu WC, Chang YL, Chen WY, Chang WC, Chien Y, Yen JC, Liu YY, Chen SJ, Wang CY, et al. Energy utilization of induced pluripotent stem cell-derived cardiomyocyte in Fabry disease. *International Journal of Cardiology*. 2017;**232**:255-263
- [68] Novak A, Barad L, Zeevi-Levin N, Shick R, Shtrichman R, Lorber A, Itskovitz-Eldor J, Binah O. Cardiomyocytes generated from CPVTD307H patients are arrhythmogenic in response to beta-adrenergic stimulation. *Journal of Cellular and Molecular Medicine*. 2012;**16**(3):468-482
- [69] Lan F, Lee AS, Liang P, Sanchez-Freire V, Nguyen PK, Wang L, Han L, Yen M, Wang Y, Sun N, et al. Abnormal calcium handling properties underlie familial hypertrophic cardiomyopathy pathology in patient-specific induced pluripotent stem cells. *Cell Stem Cell*. 2013;**12**(1):101-113
- [70] Han L, Li Y, Tchao J, Kaplan AD, Lin B, Li Y, Mich-Basso J, Lis A, Hassan N, London B, et al. Study familial hypertrophic cardiomyopathy using patient-specific induced pluripotent stem cells. *Cardiovascular Research*. 2014;**104**(2):258-269
- [71] Sadahiro T, Yamanaka S, Ieda M. Direct cardiac reprogramming: Progress and challenges in basic biology and clinical applications. *Circulation Research*. 2015;**116**(8):1378-1391
- [72] Chen O, Qian L. Direct cardiac reprogramming: Advances in cardiac regeneration. *BioMed Research International*. 2015;**2015**:580406
- [73] Chadwick AC, Musunuru K. Genome editing for the study of cardiovascular diseases. *Current Cardiology Reports*. 2017;**19**(3):22
- [74] Strong A, Musunuru K. Genome editing in cardiovascular diseases. *Nature. Reviews*. 2017;**14**(1):11-20
- [75] Chen L, Tang L, Xiang H, Jin L, Li Q, Dong Y, Wang W, Zhang G. Advances in genome editing technology and its promising application in evolutionary and ecological studies. *Gigascience*. 2014;**3**:24
- [76] Eyquem J, Mansilla-Soto J, Giavridis T, van der Stegen SJ, Hamieh M, Cunanan KM, Odak A, Gonen M, Sadelain M. Targeting a CAR to the TRAC locus with CRISPR/Cas9 enhances tumour rejection. *Nature*. 2017;**543**(7643):113-117
- [77] Duncker DJ, Bakkers J, Brundel BJ, Robbins J, Tardiff JC, Carrier L. Animal and in silico models for the study of sarcomeric cardiomyopathies. *Cardiovascular Research*. 2015;**105**(4):439-448
- [78] Waddington SN, Privolizzi R, Karda R, O'Neill HC. A broad overview and review of CRISPR-Cas technology and stem cells. *Current Stem Cell Reports*. 2016;**2**:9-20