Chapter 2

Genetic Evaluation of Hypertrophic Cardiomyopathy

Cristina Florescu

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79626

Abstract

Hypertrophic cardiomyopathy (HCM) is defined as left ventricular hypertrophy in the absence of abnormal loading conditions. In 50–60% of adolescents and adults with HCM, the disease is inherited as an autosomal dominant trait caused by mutations in cardiac sarcomere protein genes. The most cases are due to mutations in genes which determine the synthesis of myosin-binding protein C (MYBPC3) and beta-myosin heavy chain (MYH7). More rarely involved genes are those encoding myosin light chain 3 (MYL3), tropomyosin alpha-1 chain (TPM1), and cardiac troponins I and T (TNNI3, TNNT2). Mutations in genes encoding Z-disc or calcium-handling proteins account for less than 1% of cases. Multiple sarcomeric protein mutations are present in up to 5% of individuals. A further of 5% of patients have inherited metabolic or neuromuscular diseases, chromosome abnormalities, and genetic syndromes. HCM is characterized by a highly heterogeneous phenotype, highly variable intra- and interfamily expressivity and incomplete penetrance, therefore by a genotype-phenotype plasticity.

Keywords: autosomal dominant, mutations, sarcomere proteins genes, incomplete penetrance, phenotype

1. Introduction

Hypertrophic cardiomyopathy (HCM) is an important genetic heart muscle disease characterized by left ventricular hypertrophy (LVH) in the absence of an underlying systemic condition or other cardiac disease, such as valvular heart disease or arterial hypertension. HCM is a global disease characterized by a prevalence of 1:500 [1, 2]. HCM is the most frequent genetic heart disease and the most important etiology of sudden death not due to trauma in adults of young age and trained athletes in the United States [3]. The onset of HCM disease can occur at any age, from infants to old people, and symptoms usually are not present before teen age in

carriers of the specific genetic mutation [3]. HCM is the first autosomal dominant genetically transmitted condition, with clinical variability and incomplete penetrance in many cases. Clinical picture of HCM covers a large spectrum, from asymptomatic disease to evolving heart failure in years and dramatic sudden cardiac death (SCD) triggered by electrical or mechanical disorders. The most used tools for diagnosis are cardiac imaging methods, such as cardiac echography and magnetic resonance imaging. Asymmetrical hypertrophy involving the septum represents a frequent finding [4].

Histopathologic characteristics include myocyte hypertrophy and disarray and increased myocardial fibrosis [4], these lesions leading to impaired diastolic function [5]. In ~5–10% of patients, cardiac systolic function decreases over time, leading to progressive left ventricle (LV) dilatation, heart failure and, finally, burnt-out HCM, morphologically similar to dilated cardiomyopathy (DCM) [6].

2. Mechanism of disease

HCM is commonly defined as a sarcomere disease. The variants with pathogenicity were found in almost all proteins of the sarcomere [7]. The pathways of molecular alteration are augmented actin-activated ATPase activity, fragmentation of interaction between actin and myosin and force developing, and modified intramyocyte calcium signaling in cardiac cells [8]. Also, some studies found that LVH can be triggered by troubles in CaMKII Mef2 signaling pathways and transforming growth factor b (TGF-b) [9].

Phenocopies of HCM are syndromes characterized by multiorgan alteration that can also present only LVH or like a dominant trait. These syndromes are storage or metabolic diseases (cardiomyopathies), like Danon disease and Wolff-Parkinson-White syndrome [10], and Fabry disease, which is a lysosomal storage condition [11]. These disorders are characterized by vacuolar accumulation in the myocytes of glycogen or glycosphingolipids, not by cardiomyocyte disarray and fibrosis [10]. LVH can also be found in the phenotype of patients with Noonan syndrome [12] and Friedreich ataxia [13].

Almost three decades ago, mutations in the beta-myosin heavy chain gene (MYH7) [14] were discovered to cause HCM, and since then, hundreds of different disease-causing mutations have been identified in genes that encode proteins of the sarcomere, the contractile unit of the cell. [15]. This molecular etiology is involved in the most familial diseases [16] and an important part of not yet explained hypertrophy sporadically found in childhood and adult age [17, 18]. There is still need for describing other genetic causes for unexplained LVH transmitted as a Mendelian or common trait in the population.

The mechanism of disease is the modification of a unique nucleotide belonging to a protein of the sarcomere. Clinical manifestations appear later in life, even if the mutant protein is present from birth. Studies on experimental models carrying human HCM mutations uncovered the mechanisms of this disease. These models demonstrate typical features of HCM found in humans like cell increasing, cardiomyocyte disarray, and interstitial fibrosis clinically

evolving similarly with those found in humans: absence of disorder in young people and progressive expression of histopathological findings in older age.

3. The genetic background of HCM

Most HCMs are caused by a dominant gene mutation. Half of all descendants of the affected individuals will inherit the HCM gene mutation and pose a very high risk for this disease. Young carriers of the mutation often have no clinical manifestations, and the symptoms develop insidiously, comprising a hypertrophic remodeling that occurs with aging [6]. Because HCM have an age-related penetrance, the absence of disease in one assessment cannot rule out further development. Sequential clinical assessments or genetic testing of family members at risk for HCM are very important.

Mutations from 13 single genes cause HCM [15] and represent about 75% of familial HCM [18]. Mutations occur predominantly in genes encoding sarcomere proteins [19], the contractile unit of myocytes. The typically mutation sarcomere proteins are those of thick and thin filament [20] and the less commonly affected are proteins who influence or transmit sarcomere forces (sarcomere-associated or Z-disc). Most mutations described in HCM are "private," appearing only in that patient and his family. Families with HCM without any correlation have different mutations in most situations [21]. Some mutations are common for specific populations. For example, 4% of people with South Asian origin have a unique HCM mutation [22]. For diagnosing the causal mutation in every patient, we usually need an accurate sequencing of all HCM genes [23]. This issue can be realized through DNA sequencing strategies which are recently developed. The HCM genetic diagnosis is possible at several registered molecular diagnostic laboratories, listed at the National Center for Biotechnology Information GeneTests website.

Defining the pathogenic mutation in an affected family member allows for further defining and low-cost assessing of mutation in all relatives. Mutation carriers have an increased risk of developing HCM, while people with negative mutations are at no risk for the disease and do not need clinical serial evaluation.

3.1. Mutations in genes that encode sarcomere proteins

Genetic etiology of HCM covers a wide spectrum, existing approximately 900 different mutations reported in the genes that encode 8 sarcomere proteins: the beta-myosin heavy chain (MYH7), cardiac myosin C-related protein (MYPBC3), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), cardiac actin (ACTC), alpha-tropomyosin (TPM1), the essential myosin light chain (MYL3), and the regulatory myosin light chain (MYL2) [18]. Mutations in MYH7 and MYPBC3 occur most frequently and represent about 50% of HCM cases. The mutations in TNNT2, TNNI3, ACTC, TPM1, MYL3, and MYL2 represent totally less than 20% of HCM cases [24]. Mutations within these genes correlate with the disease status in the HCM families and are absent from the control populations. Mutations modify highly conserved residues throughout evolution, which means that changing each specific amino acid is deleterious—this

has been confirmed by animal models that carry mutations in the sarcomeric gene. These experimental models develop cardiac remodeling similar to human HCM. Mutations in other genes reported as causing HCM are based on weaker evidence for HCM etiology.

Gene encoding for troponin C (TNNC1) represents a sarcomere protein gene that has not been definitely involved in HCM [25]. Studies which analyzed over 1000 HCM patients described four variants of TNNC1 sequences, although genetic criteria for a pathogenic role remain unknown. Experimental models analysis of another gene variant highlighted the augmented Ca^{2+} sensitivity of force transmission and ATPase activation [25, 26], similar to the biophysical changes presenting in already defined genes for HCM.

3.2. Mutations in genes encoding Z-disc proteins

Genes encoding molecules that interact with sarcomeric proteins have also been investigated for HCM mutations. Many of these analyses focus on proteins located in the Z disc, which bind sarcomere units. Other variants have been discovered in genes encoding titin (TTN) [27], LIM muscle protein (CSRP) [28, 29], telethonin (TCAP) [30] and myozenin 2 (MYOZ2) [31]. Analysis of sequence was referring only to the subsets of the 363 exons encompassing titin, which represents a giant molecular structure in the sarcomere laying from the Z-disc to the M-line, but the screening for other mutant proteins in the Z-disc is more complete. Functional studies of newly identified variants indicate that they alter protein-protein interactions. For example, the modified titin residues that have been identified have increased binding affinity for actinin [27, 32] or for cardiac ankyrin repeat protein [33]. The pathogenic role of some variants in HCM remains inconsistent because sequence variants in Z-disc proteins identified in some HCM families are not large enough to provide statistically significant analyses.

3.3. Storage cardiomyopathies simulating HCM

Patients with left ventricular hypertrophy (LVH) of unknown etiology and atypical clinical manifestations from those with HCM helped identify storage cardiomyopathy and disorders that have distinct molecular etiologies. Mutations in the gamma-subunit of the AMP-dependent protein kinase gene (PRKAG2) cause LVH that is inherited as a dominant feature, in which cardiac histopathology shows a marked accumulation of glycogen in myocytes and not myocyte disarray [10]. Patients with PRKAG2 mutations also have electrophysiological disorders and develop progressive disease of the conduction system. Mutations in the X-linked lysosome-associated membrane protein 2 (LAMP2) cause early and important LVH in boys and male teenagers, severe ventricular arrhythmias, and rapid evolution to cardiac failure. LAMP2 mutations demonstrate at histopathological examination accumulation of vacuoles filled with non-degraded cellular products resulting from autophagy [10]. Fabry disease is produced by mutations in a gene located on X chromosomes, which encodes alpha-galactosidase (GAA). These patients commonly demonstrate ventricular hypertrophy in addition to systemic involvement. The most patients develop myocardial disease [34], while renal, neurological, and cutaneous changes are subclinical.

All these storage cardiomyopathies are accompanied by cardiac hypertrophy. Considering histopathological differences with HCM, distinct clinical phenotypes, and different functions of mutated molecules, these disorders are considered distinct from HCM.

4. Clinical gene-related diagnosis of HCM

An important clinical progress resulting from the discovery of the genetic causes of HCM is gene-based diagnosis. Given the overlapping clinical phenotype of unexplained LVH that arises from various cardiomyopathies and the lack of clinical manifestations to accurately predict the implication of a particular HCM gene, gene-based diagnostic platforms required the general query of all sarcomere genes, sarcomere-related genes, and genes causing storage cardiomyopathies; this technically difficult task is, until recently, very expensive and laborious. With the next-generation sequencing development, many obstacles have diminished.

Contemporary sequencing strategies have the ability to query millions of nucleotides at a reasonable cost. An additional advantage is that these platforms define the genetic sequence and also the dose of genes. Recent findings indicate that mutations that modify the number of gene copies can lead to conditions like congenital heart diseases, neurological and cognitive diseases, and neoplasia [35, 36]. A few HCM may appear from an abnormal number of genetic copies (by increasing or decreasing the dosage of the gene). The absence of a specific mutation in some patients with HCM could be explained by existence of mutations that modulate gene dose in HCM and thus a leakage of detection by classical sequencing methods. This concept that HCM might be provoked by modified dosage of sarcomere protein genes is particularly challenging due to the fact that some mutations in the MYPBC3 gene have been shown to cause disease by decreasing protein levels [37, 38]. Another cause of HCM might be mutations that modified the quantity of the MYPBC3 gene and perhaps other sarcomere protein genes which could significantly affect protein levels.

5. Links between genetic testing and phenotype in HCM

One of the many advances that may result from large-scale genetic testing in HCM is better assessment of genotype relevance in the phenotype. HCM genetic testing, recognized to accurately predict disease progression in at-risk relatives, cannot predict the clinical course for each patient. It is possible that the number of HCM genotyped patients remains too modest to explore these correlations, particularly based on genetic heterogeneity and the influence that modifiers such as background genotypes [39], gender [40], and the environment [41]. Clinical course is recognized as more adverse in patients with HCM with an identified mutation than patients without mutation [42]. Some specific mutations can affect the evolution. Sudden cardiac death appears more frequently in MYH7 specific mutations (R403Q, R453C, G716R and R719W) [43], and progression to heart failure is more commonly seen in MYH7 (R719W), TNNI3 (deletion Lys183), and MYPBC3 (intron 32 mutations deletion) than in other HCM mutations [22, 44]. Understanding of the full range of HCM genes together with the molecular genetic analysis of well-investigated patient cohorts can contribute to develop these links and improve knowledge of clinical differences in HCM.

The age at which the signs and symptoms of HCM appear are influenced by causal gene mutation [15, 19]. Clinical manifestations of HCM caused by mutations in the heavy β-myosin or troponin T chain usually begin in adolescence [21, 45]. In contrast, myosin-linked protein C

mutations, especially those that inhibit the protein, trigger HCM after a prolonged period of clinical quiescence that can extend to middle age [46, 47].

The various genetic causes of HCM do not correlate with the size or distribution of hypertrophy, with some notable exceptions. Troponin T mutations generally generate much lower hypertrophy than other HCM genes, and genetic diagnosis is useful in determining the status of individuals at risk of inheriting these mutations [45]. The different morphological models of HCM hypertrophy (asymmetric, concentric, or apical) do not refer to the underlying genotype, except for a single actin mutation that produces uniform apical hypertrophy [48]. Factors that involve morphological pattern remain unknown.

The natural history of HCM includes dyspnea and progressive angina. These symptoms reflect a noncompliant myocardium, increased ventricular diastolic pressure, and impaired diastolic filling [6, 41, 49, 50]. The anatomy of coronary artery tree is normal in HCM but mechanism of myocardial ischemia in HCM consists of decrease of blood flow in diastole due to intramural arterial remodeling and impaired myocardial relaxation [51]. Approximately 5% of patients with HCM appear severe diastolic dysfunction which can be accompanied in time by contractile insufficiency of the myocardium [52].

Patients with a genetic mutation of the defined sarcomeric protein have lower cardiac output than those whose HCM etiology remains unknown [42]. In addition, it was shown that HCM specific mutations [53], compound mutations [54], and a mutation that is predominant among patients of Indian origin [22] substantially increase the risk of developing heart failure.

6. Cardiac hypertrophy mechanisms in HCM

6.1. Alteration in sarcomere function

Several models have been proposed for mechanisms of myocardial hypertrophy by mutations of the sarcomere genes. Recent analyses in human cardiac samples and experimental models show that concentration of myosin-binding protein C is reduced in the myocardium of patients with MYBPC3 missense amino acid residues and truncation mutations [37, 38]. This information indicates that MYBPC3 haploinsufficiency or a decrease in the quantity of functional protein due to a dominant gene mutation that inactivates an allele acts as a pathological mechanism for HCM. In contrast, studies on most other sarcomere mutations indicate that these influence on the fact that protein levels are normal, but its function is disturbed. The biophysical properties of sarcomeres carrying MYH7 mutations indicate an increase in function. Myosines containing HCM mutations improved the ATPase activity of myosines, increased the force generated, and accelerated the actin filament gliding [55]. Analyses of human TNNT2 mutations indicate that these anomalies show an increase in contraction [56] and ATPase activation [57].

The consequences of changes in the biophysical properties of contractile proteins could significantly influence sarcomere performance, myocardial cell biology, and myocardial energy.

Due to the presence of both mutant and normal proteins within sarcomeres, regulated contractions would become discoordinated, as shown with HCM myosin mutations: HCM mutation MYH7 R403Q is attached to the actin at angles highly variable compared to the normal myosin [58]. Biophysical changes of mutant sarcomeres are also expected to modify the calcium cycling and contribute to increased susceptibility to arrhythmia in experimental and human HCM [59]. The increase in ATPase activity by sarcomere mutations can also cause a higher consumption of myocardial energy, which may accelerate the death of cardiomyocytes and may contribute to focal fibrosis and scarring described in HCM [60].

6.2. Activation of Ca^{2+}-dependent signaling in HCM

Dysregulation of intracellular Ca^{2+}, a pivotal modulator of myocardial contraction and relaxation, can trigger hypertrophy and failure in this stressed myocardium [61]. Experimental models of HCM myocytes exhibit abnormal intracellular Ca^{2+}, including low sarcoplasmic reticulum levels and elevated diastolic Ca^{2+} concentration [56, 62]. In HCM models, Ca^{2+} disorders precede hypertrophic remodeling. Some longitudinal studies demonstrate that initial pharmacological therapy that normalized Ca^{2+} abnormalities has decreased the development of hypertrophy [62]. An important yet unclarified idea raised by this is which hypertrophic mechanisms are stimulated by Ca^{2+} dysregulation in HCM cardiomyocytes?

In experimental studies on hypertrophy induced by pressure overload, intracellular Ca^{2+} triggered activation of calmodulin and calcineurin, its phosphatase, which produce dephosphorylation, and activated NFAT (nuclear factor of activated T cell) transcriptional factor, a known molecule involved in hypertrophic remodeling [63]. Calcineurin inhibitors, like cyclosporin, inhibit hypertrophy induced by overexpression of calcineurin in the hearts [64]. However, cyclosporin administered to HCM mice has a very different effect: rapidly evolving pathological remodeling and cardiac insufficiency [65]. The pathways which provoke the stimulation of calcineurin in HCM are not yet understood and some studies have shown a critical role for Ca^{2+}-dependent signaling in HCM pathogenesis. These data have promoted studies of prevention addressed to normalizing Ca^{2+} dysregulation in HCM models. Young HCM mice (myosin R403Q), without any proof of hypertrophy, were treated with L-channel type Ca^{2+} blocker, diltiazem. This resulted in intracellular Ca^{2+} levels normalization and important inhibition of development of cardiac hypertrophy [62], suggesting that targeting key intracellular events in the development of HCM pathology could prevent the development of the disease.

6.3. HCM enhances myocyte stress

Modified biophysical forces and intracellular Ca^{2+} in HCM myocytes, as well as increased energy demands, promote increased stress on HCM myocytes. Moreover, microvascular dysfunction, demonstrated by positron emission tomography (PET) and cardiovascular magnetic resonance (CMR) in HCM patients [66, 67], may cause ischemia in HCM. In addition, factors that increase myocardial stress are supposed to promote death of myocytes and lead to myocardial scarring in HCM [68].

Molecular analyses also support increased myocyte stress in HCM. In HCM models [69] and human HCM hearts, fetal heart genes are found. These genes are normally repressed after embryonic development but are re-expressed with myocyte stress [70]. Lipid peroxide levels, indicating oxidative stress, are also elevated in HCM models [71]. Studies of mechanism implicated in oxidative stress in HCM hearts exhibit thio-responsive pathways, an observation that determined the study of N-acetylcysteine in HCM models. High concentration of this substance decreased biochemical markers of oxidative stress and surprisingly demonstrated the reversal of fibrosis in HCM models [60, 72]. The potential favorable effect of antioxidants in human HCM requires further studies.

7. Clinical testing and genetic etiology

Pathogenic variants for HCM were originally described in eight genes encoding sarcomere proteins, with most (~80%) present in the MYH7 and MYBPC3 genes [3, 73]. Typically for these structural proteins, most sarcomere variants act in a dominant negative way (by negatively affecting the normal gene product). Loss-of-function variants that lead to haploinsufficiency appear less frequently, predominantly in the MYBPC3 gene [74]. Sarcomeric variants are identified in up to 60% of HCM patients with a family history and in approximately 40% of patients with sporadic HCM [75]. Storage cardiomyopathies that mimic HCM are caused by mutations in GLA (Fabry disease), LAMP2 (Danon disease), and PRKAG2 (Wolff-Parkinson-White syndrome).

The HCM-associated gene spectrum has been developed in nonarrhythmic genes and includes genes encoding Z-disc proteins and proteins localized in the plasma membrane and sarcoplasmic reticulum. Variants in these genes are rare, with limited studies supporting evidence of a role in the disease. Some genes are associated with strong genetic evidence such as segregation with disease or functional data in vivo (e.g. CSRP3) [29], but many genes (e.g. MYH6, MYLK2, and TCAP) are only supported by the presence of variants in affected individuals and the absence from controls. These genes are better considered candidate genes. Almost 1000 HCM variants have been diagnosed so far [75], most of which being unique or private, and can only be identified through a comprehensive genetic evaluation. A small number of recurrent variants are detected at larger population frequencies; the most frequent being a 25 bp deletion in the intron 32 of MYBPC3 gene, which is predominant in Southeast Asian populations (~4%) and increases risk of heart failure with an odds ratio of ~7 [45].

With few exceptions, genotype-phenotype correlations for HCM are incompletely defined. Some, but not all, TNNT2 mutations are associated only with minor hypertrophy, but with an appreciable risk of arrhythmia [45]. MYH7 variants generally appear to promote significant LVH that is evident in the second decade of life and are believed to be associated with an increased risk of heart failure and SCD [76]. Pathogenic variants in MYBPC3 are believed to be associated with a later onset [47]. These variants were also identified in a significant proportion of patients with early onset LVH in childhood [18]. Most variants of MYBPC3 in the pediatric population were missense mutations that contrasted with the high prevalence of

identified loss-of-function variants in HCM adult patients and suggest that missense variants may have worse functional consequences [18].

The US HCM Guidelines recommend complete testing for five HCM genes (MYBPC3, MYH7, TNNI3, TNNT2, and TPM1) [77]. Sequencing diagnostic panels, including these genes, are offered by several laboratories around the world.

In fact, genetic testing for HCM is mainly used to identify families with a detectable genetic cause of the disease and to examine family members at risk. Testing can also help to exclude nongenetic conditions, such as the heart of the athlete, though in case of an identification of a pathogenic variant [75, 78]. Due to the absence of clear genotype-phenotype links, the genetic test results in clinical management guidance have limited usefulness. The exception is enzyme replacement treatment for storage diseases that may have isolated LVH [79, 80].

An area under development is the use of genotype analysis to guide treatment decisions in preclinical HCM patients. Experimental animal studies suggest that some calcium channel blockers, such as diltiazem, may influence by delaying the clinical progression of HCM [62].

Studies in animals have also led to a link between sarcomeric HCM and increase in transforming growth factor b signaling. An anti-transforming growth factor b antibody and losartan (a type 1 angiotensin II receptor antagonist) prevented cardiac fibrosis and hypertrophy in sarcomere mutation-positive mice, which may suggest additional therapeutic possibilities [9].

Since the discovery that pathogenic variants in sarcomeric genes cause HCM [7], much progress has been made to define the genetic etiology of inherited cardiomyopathies. The high risk of SCD in patients with this disorder has encouraged interest in clinical genetic testing. All cardiomyopathies are characterized by a high heterogeneity linked to the great number of loci and allele that require sequential analysis of the entire coding region of several genes, which has been an expensive and long-lasting process using classical technologies. Genetic and phenotypic overlapping between different cardiomyopathies is increasing and this assumes more difficulties, often leading to testing more cardiomyopathy-specific gene panels when the diagnosis is not entirely known. The next-generation sequencing technologies (NGS) have eliminated these problems and allowed the concomitant investigation of a multitude of genes. A negative effect of this possibility of sequencing any gene is an increased likelihood of detecting variants of unclear clinical significance (VUSs). This disadvantage requiring a strict review of the proofs supporting the signs of disorder association as variants in poorly studied genes can be difficult to estimate. There were described variants in >50 genes to be causal for various inherited cardiac muscle diseases, but a comprehensive review shows that only half of them meet the criteria to be considered a definitive gene of the disease.

Current practice guidelines and expert opinions on clinical approach and genetic diagnosis for inherited cardiomyopathies recommend taking a detailed family history that includes at least three generations, clinical screening of at-risk family members, counseling patients about the possibility of an inherited cause, and examining by genetic testing the most obvious affected persons in the family [77]. The recommendations of specific or comprehensive genetic testing are established by the guidelines for only a small number of genes [77], in opposition to the growing use of large gene panels in clinical practice.

For inherited cardiomyopathies, the treatment possibilities are very few and the clinical utility of genetic testing is based on the capacity to confirm the etiology of the disease in proband (when a known pathogenic variant is identified). Subsequent genetic testing of at-risk family members can eliminate the risk of disease (when negative) or identify those members who require monitoring or clinical intervention to reduce the risk of morbidity or mortality (when positive). The spectrum of pathogenic variants present in the population is incompletely characterized, even in well-known disease genes, with a high probability of detecting a new VUS sequence that can create emotional stress for patients [80].

8. Genotype-phenotype overlap between inherited cardiomyopathies

Cardiomyopathies were classically classified only based on clinical features, including ventricular morphology and function. Although HCM, DCM, and arrhythmogenic right ventricular cardiomyopathy (ARVC) are distinct clinical diseases, there is an increasing observation of substantial genetic and phenotypic overlapping. There are phenotypic overlaps between HCM in the final stage and DCM [81] and between DCM and ARVC (which may be manifested by ventricular dilatation and VS involvement) [82]. Also, left ventricular noncompaction (LVNC) features may overlap with those of HCM, DCM, and restrictive cardiomyopathy (RCM) [83].

The genetic etiologies underlying these conditions are clarified and the overlapping results increase substantially. Pathogenic sarcomere variants have been identified first in HCM patients, but also in patients with DCM, LVNC, and RCM [80].

Z-disc mutation genes were involved in DCM and HCM [84]. Desmosomal protein genes were originally thought to be involved only in ARVC, and the evidence suggests that variants in these genes can also lead to DCM [85]. The phenotypic spectrum of variants in the desmin gene includes DCM, RCM, and, most recently described, ARVC [86–88]. Variants of the cardiac troponin T (TTN) gene have recently been shown to be a frequent etiology of DCM, but growing evidence also associates this gene with ARVC [89].

Although it is established that variants in a particular gene may lead to more than one cardiomyopathy, it has been investigated whether the responsible variants are different. Some studies have discovered the same variant in patients with HCM and in patients with DCM, this fact being attributed to phenotypic plasticity [90, 91]. However, the background molecular mechanisms of HCM (high contractility) and DCM (low contractility) are extremely different, which raises questions as to whether the same variant can indeed cause both diseases [80]. Functional characterization of several HCM and DCM variants revealed opposite fundamental properties, supporting distinct variants [92–94]. Assuming nonoverlapping variants, identification of HCM variants in patients with marked LV dilatation and impaired systolic function may reflect remodeling in the final phase of HCM rather than primary DCM. Another explanation for identifying one and the same variant in disorders with distinct molecular mechanisms is that they are not the principal or initial cause of the disease but act as modifiers

or are completely benign. We have now the possibility to evaluate the spectrum of rare benign variations since we are able to query thousands of sequenced genomes and exomes (1000 Genomes Project, National Heart, Lung and Blood Institute Exome Sequencing Project). A disadvantage was the fact that many studies in the past have inferred gene pathogenicity based on insufficient proofs. This has recently been demonstrated for a lot of published variants that have been reported to determine DCM [95]. One example illustrating the temporal evolution of a variant is the Ala833Thr variant of MYBPC3, which was originally reported in four HCM probands and 1 in 400 control individuals [74, 96, 97]. Its presence in a single control person was considered insufficient to exclude a pathogenic role because low penetration is quite frequent in HCM. It is already discovered that this variant is present in 12 of 6952 chromosomes (0.17% Exome Sequencing Project from the Heart, Lung and Blood National Institute), demonstrating the importance of extensive genomic sequencing studies and clearly suggesting that there is a low probability for this variant to be a primary cause of HCM.

In conclusion, it seems probably that the individual variants are most commonly specific to one cardiomyopathy presentation, and new studies that include more precise phenotypic testing and classification of the genetic variants can be useful to prove this with certainty (**Table 1**).

Gene	Location	Inheritance	Muscular component	Gene product
MYH7	14q11.2	AD	Thick filament	β-Myosin heavy chain
MYL3	3p21.31	AD	Thick filament	Essential myosin light chain
MYL2	12q24.11	AD	Thick filament	Regulatory myosin light chain
TTN	2q31.2	AD	Thick filament	Titin
MYH6	14q11.2	AD	Thick filament	α-Myosin heavy chain
TNNT2	1q32.1	AD	Thin filament	Cardiac troponin T
TNNC1	3p21.1	AD	Thin filament	Cardiac troponin C
TNNI3	19q13.42	AD	Thin filament	Cardiac troponin I
ACTC		AD	Thin filament	α-Cardiac actin
TPM1	15q22.2	AD	Thin filament	α-Tropomyosin
MYBPC3	11p11.2	AD	Intermediate filament	Cardiac myosin-binding protein C
CASQ2	1p13.1	AR	Calcium handling	Calsequestrin
JPH2	20q13.12	AD	Calcium handling	Junctophilin 2
MYOZ2	4q26	AD	Z-disc	Myozenin2
ACTN2	1q43	AD	Z-disc	α-Actinin2
VCL	10q22.2	AD	Z-disc	Vinculin/metavinculin
TCAP	17q12	AR, AD	Z-disc	Telethonin
CSRP3	11p15.1	AD	Z-disc	Muscle LIM protein

Table 1. Genes having pathogenicity for hypertrophic cardiomyopathy [98–100].

9. Conclusions

For an optimal approach of patients with HCM, genetic testing is available and very useful. Major progresses have been made with the finding of several mutations that have demonstrated marked genotypic and phenotypic heterogeneity of this cardiac muscle disorder. This genetic testing must be performed in certified diagnostic laboratories. The first indication is for testing patients who have completed the diagnostic criteria for HCM, allowing further screening of the family members. Some other potential advantages are confirming or infirming the diagnosis in ambiguous situations and allowing a better understanding of this polymorphic disease.

Conflict of interest

None.

Author details

Cristina Florescu

Address all correspondence to: tohaneanu67@yahoo.com

Craiova University of Medicine and Pharmacy, Craiova, Romania

References

[1] Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults: Echocardiographic analysis of 4111 subjects in the CARDIA study. Circulation. 1995;**92**:785-789

[2] Zou Y, Song L, Wang Z, Ma A, Liu T, Gu H, Lu S, Wu P, Zhang Y, Shen L, Cai Y, Zhen Y, Liu Y, Hui R. Prevalence of idiopathic hypertrophic cardiomyopathy in China: A population-based echocardiographic analysis of 8080 adults. The American Journal of Medicine. 2004;**116**:14-18

[3] Maron BJ, Casey SA, Hauser RG, Aeppli DM. Clinical course of hypertrophic cardiomyopathy with survival to advanced age. Journal of the American College of Cardiology. 2003;**42**:882-888

[4] Cirino AL and Ho C. Familial Hypertrophic Cardiomyopathy Over-view. In: GeneReviews [Internet]. Copyright University of Washington, Seattle. 1993-2012. Available at www.genetests.org., Last Revised May 17, 2011

[5] Maron BJ, Roberts WC. Quantitative analysis of cardiac muscle cell disorganization in the ventricular septum of patients with hypertrophic cardiomyopathy. Circulation. 1979;**59**:689-706

[6] Maron BJ. Hypertrophic cardiomyopathy: A systematic review. JAMA. 2002;**287**:1308-1320

[7] Seidman CE, Seidman JG. Identifying sarcomere gene mutations in hypertrophic cardiomyopathy: A personal history. Circulation Research. 2011;**108**:743-750

[8] Fatkin D, Graham RM. Molecular mechanisms of inherited cardiomyopathies. Physiological Reviews. 2002;**82**:945-980

[9] Teekakirikul P, Eminaga S, Toka O, Alcalai R, Wang L, Wakimoto H, Nayor M, Konno T, Gorham JM, Wolf CM, Kim JB, Schmitt JP, Molkentin JD, Norris RA, Tager AM, Hoffman SR, Markwald RR, Seidman CE, Seidman JG. Cardiac fibrosis in mice with hypertrophic cardiomyopathy is mediated by non-myocyte proliferation and requires Tgf-b. The Journal of Clinical Investigation. 2010;**120**:3520-3529

[10] Arad M, Maron BJ, Gorham JM, Johnson WH Jr, Saul JP, Perez-Atayde AR, Spirito P, Wright GB, Kanter RJ, Seidman CE, Seidman JG. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. The New England Journal of Medicine. 2005;**352**:362-372

[11] Sachdev B, Takenaka T, Teraguchi H, Tei C, Lee P, McKenna WJ, Elliott PM. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. Circulation. 2002;**105**:1407-1411

[12] Nishikawa T, Ishiyama S, Shimojo T, Takeda K, Kasajima T, Momma K. Hypertrophic cardiomyopathy in Noonan syndrome. Acta Paediatrica Japonica. 1996;**38**:91-98

[13] Osterziel KJ, Bit-Avragim N, Bunse M. Cardiac hypertrophy in Friedreich's ataxia. Cardiovascular Research. 2002;**54**:694. Author Reply 695-696

[14] Geisterfer-Lowrance AA, Kass S, Tanigawa G, et al. A molecular basis for familial hypertrophic cardiomyopathy: A beta cardiac myosin heavy chain gene missense mutation. Cell. 1990;**62**:999-1006

[15] Alcalai R, Seidman JG, Seidman CE. Genetic basis of hypertrophic cardiomyopathy: From bench to the clinics. Journal of Cardiovascular Electrophysiology. 2008;**19**:104-110

[16] Richard P, Charron P, Carrier L, et al. Hypertrophic cardiomyopathy: Distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. Circulation. 2003;**107**:2227-2232

[17] Morita H, Larson MG, Barr SC, et al. Single-gene mutations and increased left ventricular wall thickness in the community: The Framingham heart study. Circulation. 2006;**113**:2697-2705

[18] Morita H, Rehm HL, Menesses A, McDonough B, Roberts AE, Kucherlapati R, et al. Shared genetic causes of cardiac hypertrophy in children and adults. The New England Journal of Medicine. 2008;**358**:1899-1908

[19] Keren A, Syrris P, McKenna WJ. Hypertrophic cardiomyopathy: The genetic determinant of clinical disease expression. Nature Clinical Practice. Cardiovascular Medicine. 2008;**5**:158-168

[20] Marian AJ. Genetic determinants of cardiac hypertrophy. Current Opinion in Cardiology. 2008;**23**:199-205

[21] Watkins H, Ashrafian H, McKenna WJ. The genetics of hypertrophic cardiomyopathy: Teare redux. Heart. 2008;**94**:1264-1268

[22] Dhandapany PS, Sadayappan S, Xue Y, et al. A common MYBPC3 (cardiac myosin binding protein C) variant associated with cardiomyopathies in South Asia. Nature Genetics. 2009;**41**(2):187-191

[23] Hershberger RE, Cowan J, Morales A, Siegried JD. Progress with genetic cardiomyopathies: Screening, counseling, and testing in dilated, hypertrophic, and arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation. Heart Failure. 2009;**2**:253-261

[24] 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**:201-211

[25] Landstrom AP, Parvatiyar MS, Pinto JR, Marquardt ML, et al. Molecular and functional characterization of novel hypertrophic cardiomyopathy susceptibility mutations in TNNC1-encoded troponin C. Journal of Molecular and Cellular Cardiology. 2008;**45**:281-288

[26] Pinto JR, Parvatiyar MS, Jones MA, et al. A functional and structural study of troponin C mutations related to hypertrophic cardiomyopathy. The Journal of Biological Chemistry. 2009;**284**:19090-19100

[27] Satoh M, Takahashi M, Sakamoto T, et al. Structural analysis of the titin gene in hypertrophic cardiomyopathy: Identification of a novel disease gene. Biochemical and Biophysical Research Communications. 1999;**262**:411-417

[28] Geier C, Perrot A, Ozcelik C, et al. Mutations in the human muscle LIM protein gene in families with hypertrophic cardiomyopathy. Circulation. 2003;**107**:1390-1395

[29] Geier C, Gehmlich K, Ehler E, et al. Beyond the sarcomere: CSRP3 mutations cause hypertrophic cardiomyopathy. Human Molecular Genetics. 2008;**17**:2753-2765

[30] Hayashi T, Arimura T, Itoh-Satoh M, et al. Tcap gene mutations in hypertrophic cardiomyopathy and dilated cardiomyopathy. Journal of the American College of Cardiology. 2004;**44**:2192-2201

[31] Osio A, Tan L, Chen SN, et al. Myozenin 2 is a novel gene for human hypertrophic cardiomyopathy. Circulation Research. 2007;**100**:766-768

[32] Matsumoto Y, Hayashi T, Inagaki N, et al. Functional analysis of titin/connectin N2-B mutations found in cardiomyopathy. Journal of Muscle Research and Cell Motility. 2005;**26**:367-374

[33] Arimura T, Matsumoto Y, Okazaki O, et al. Structural analysis of obscurin gene in hypertrophic cardiomyopathy. Biochemical and Biophysical Research Communications. 2007;**362**(2):281-287

[34] Nakao S, Takenaka T, Maeda M, et al. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. The New England Journal of Medicine. 1995;**333**:288-293

[35] Wain LV, Armour JA, Tobin MD. Genomic copy number variation, human health, and disease. Lancet. 2009;**374**:340-350

[36] Hastings PJ, Lupski JR, Rosenberg SM, Ira G. Mechanisms of change in gene copy number. Nature Reviews. Genetics. 2009;**10**:551-564

[37] van Dijk SJ, Dooijes D, dos Remedios C, et al. Cardiac myosin-binding protein C mutations and hypertrophic cardiomyopathy: Haploinsufficiency, deranged phosphorylation, and cardiomyocyte dysfunction. Circulation. 2009;**119**:1473-1483

[38] Marston S, Copeland O, Jacques A, Livesey K, et al. Evidence from human myectomy samples that MYBPC3 mutations cause hypertrophic cardiomyopathy through haploinsufficiency. Circulation Research. 2009;**105**:219-222

[39] Perkins MJ, Van Driest SL, Ellsworth EG, et al. Gene-specific modifying effects of pro-LVH polymorphisms involving the renin-angiotensin-aldosterone system among 389 unrelated patients with hypertrophic cardiomyopathy. European Heart Journal. 2005; **26**:2457-2462

[40] Bos JM, Theis JL, Tajik AJ, et al. Relationship between sex, shape, and substrate in hypertrophic cardiomyopathy. American Heart Journal. 2008;**155**:1128-1134

[41] Maron BJ, McKenna WJ, Danielson GK, et al. Task force on clinical expert consensus documents. American College of Cardiology; Committee for Practice Guidelines. European Society of Cardiology. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation task force on clinical expert consensus documents and the European Society of Cardiology Committee for practice guidelines. Journal of the American College of Cardiology. 2003;**42**:1687-1713

[42] Olivotto I, Girolami F, Ackerman MJ, et al. Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. Mayo Clinic Proceedings. 2008;**83**:630-638

[43] Ackerman MJ, VanDriest SL, Ommen SR, et al. Prevalence and age-dependence of malignant mutations in the beta-myosin heavy chain and troponin T genes in hypertrophic cardiomyopathy: A comprehensive outpatient perspective. Journal of the American College of Cardiology. 2002;**39**:2042-2048

[44] Kokado H, Shimizu M, Yoshio H, et al. Clinical features of hypertrophic cardiomyopathy caused by a Lys183 deletion mutation in the cardiac troponin I gene. Circulation. 2000;**102**:663-669

[45] Watkins H, McKenna WJ, Thierfelder L, Suk HJ, Anan R, O'Donoghue A, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. The New England Journal of Medicine. 1995;**332**:1058-1064

[46] Niimura H, Bachinski LL, Sangwatanaroj S, Watkins H, Chudley AE, McKenna W, et al. Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. The New England Journal of Medicine. 1998;**338**:1248-1257

[47] Niimura H, Patton KK, McKenna WJ, Soults J, Maron BJ, Seidman JG, et al. Sarcomere protein gene mutations in hypertrophic cardiomyopathy of the elderly. Circulation. 2002;**105**:446-451

[48] Arad M, Penas-Lado M, Monserrat L, Maron BJ, Sherrid M, Ho CY, et al. Gene mutations in apical hypertrophic cardiomyopathy. Circulation. 2005;**112**:2805-2811

[49] Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. Lancet. 2004;**363**:1881-1891

[50] Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. The New England Journal of Medicine. 1997;**336**:775-785

[51] Camici PG, Crea F. Coronary microvascular dysfunction. The New England Journal of Medicine. 2007;**356**:830-840

[52] Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation. 2006;**114**:216-225

[53] Anan R, Greve G, Thierfelder L, Watkins H, McKenna WJ, Solomon S, et al. Prognostic implications of novel beta cardiac myosin heavy chain gene mutations that cause familial hypertrophic cardiomyopathy. The Journal of Clinical Investigation. 1994;**93**:280-285

[54] Ingles J, Doolan A, Chiu C, Seidman J, Seidman C, Semsarian C. Compound and double mutations in patients with hypertrophic cardiomyopathy: Implications for genetic testing and counselling [letter]. Journal of Medical Genetics. 2005;**42**:e59

[55] Tyska MJ, Hayes E, Giewat M, et al. Single-molecule mechanics of R403Q cardiac myosin isolated from the mouse model of familial hypertrophic cardiomyopathy. Circulation Research. 2000;**86**:737-744

[56] Guinto PJ, Haim TE, Dowell-Martino CC, et al. Temporal and mutation-specific alterations in Ca^{2+} homeostasis differentially determine the progression of cTnT-related cardiomyopathies in murine models. American Journal of Physiology. Heart and Circulatory Physiology. 2009;**297**:H614-H626

[57] Hernandez OM, Szczesna-Cordary D, Knollmann BC, et al. F110I and R278C troponin T mutations that cause familial hypertrophic cardiomyopathy affect muscle contraction in transgenic mice and reconstituted human cardiac fibers. The Journal of Biological Chemistry. 2005;**280**:37183-37194

[58] Volkmann N, Lui H, Hazelwood L, et al. The R403Q myosin mutation implicated in familial hypertrophic cardiomyopathy causes disorder at the actomyosin interface. PLoS One. 2007;**2**:e1123

[59] Baudenbacher F, Schober T, Pinto JR, et al. Myofilament Ca^{2+} sensitization causes susceptibility to cardiac arrhythmia in mice. The Journal of Clinical Investigation. 2008;**118**: 3893-3903

[60] Lombardi R, Rodriguez G, Chen SN, et al. Resolution of established cardiac hypertrophy and fibrosis and prevention of systolic dysfunction in a transgenic rabbit model of human cardiomyopathy through thiol-sensitive mechanisms. Circulation. 2009;**119**:1398-1407. This report showed that reducing oxidative stress in a rabbit model of HCM decreased hypertrophy and fibrosis. If confirmed in human patients, this would provide new treatment strategies in HCM

[61] Backs J, Backs T, Neef S, et al. The delta isoform of CaM kinase II is required for pathological cardiac hypertrophy and remodeling after pressure overload. Proceedings of the National Academy of Sciences of the United States of America. 2009;**106**:2342-2347

[62] Semsarian C, Ahmad I, Giewat M, et al. The L-type calcium channel inhibitor diltiazem prevents cardiomyopathy in a mouse model. The Journal of Clinical Investigation. 2002;**109**:1013-1020

[63] Czubryt MP, Olson EN. Balancing contractility and energy production: The role of myocyte enhancer factor 2 (MEF2) in cardiac hypertrophy. Recent Progress in Hormone Research. 2004;**59**:105-124

[64] Molkentin JD, Lu JR, Antos CL, et al. A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. Cell. 1998;**93**:215-228

[65] Fatkin D, McConnell BK, Mudd JO, et al. An abnormal Ca(2+) response in mutant sarcomere protein-mediated familial hypertrophic cardiomyopathy. The Journal of Clinical Investigation. 2000;**106**:1351-1359

[66] Petersen SE, Jerosch-Herold M, Hudsmith LE, et al. Evidence for microvascular dysfunction in hypertrophic cardiomyopathy: New insights from multiparametric magnetic resonance imaging. Circulation. 2007;**115**:2418-2425

[67] Maron MS, Olivotto I, Maron BJ, et al. The case for myocardial ischemia in hypertrophic cardiomyopathy. Journal of the American College of Cardiology. 2009;**54**:866-875

[68] Ino T, Nishimoto K, Okubo M, Sueyoshi N, et al. Apoptosis as a possible cause of wall thinning in end-stage hypertrophic cardiomyopathy. The American Journal of Cardiology. 1997;**79**:1137-1141

[69] Kim JB, Porreca GJ, Song L, et al. Polony multiplex analysis of gene expression (PMAGE) in mouse hypertrophic cardiomyopathy. Science. 2007;**316**:1481-1484

[70] Hasegawa K, Fujiwara H, Doyama K, et al. Ventricular expression of brain natriuretic peptide in hypertrophic cardiomyopathy. Circulation. 1993;**88**:372-380

[71] Senthil V, Chen SN, Tsybouleva N, et al. Prevention of cardiac hypertrophy by atorvastatin in a transgenic rabbit model of human hypertrophic cardiomyopathy. Circulation Research. 2005;**97**:285-292

[72] Konno T, Chang S, Seidman JG, Seidman CE. Genetics of hypertrophic cardiomyopathy. Current Opinion in Cardiology. 2010;**25**(3):205-209

[73] Callis TE, Jensen BC, Weck KE, Willis MS. Evolving molecular diagnostics for familial cardiomyopathies: At the heart of it all. Expert Review of Molecular Diagnostics. 2010;**10**:329-351

[74] Andersen PS, Havndrup O, Bundgaard H, Larsen LA, Vuust J, Pedersen AK, Kjeldsen K, Christiansen M. Genetic and phenotypic characterization of mutations in myosin-binding protein C (MYBPC3) in 81 families with familial hypertrophic cardiomyopathy: Total or partial haploinsufficiency. European Journal of Human Genetics. 2004;**12**:673-677

[75] Ho CY. Genetics and clinical destiny: Improving care in hypertrophic cardiomyopathy. Circulation. 2010;**122**:2430-2440. discussion 2440

[76] Ho CY. Hypertrophic cardiomyopathy. Heart Failure Clinics. 2010;**6**:141-159

[77] Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP. HRS/EHRA expert consensus statement on the state of genetic testing for the chan-nelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011;**8**:1308-1339

[78] Wheeler M, Pavlovic A, DeGoma E, Salisbury H, Brown C, Ashley EA. A new era in clinical genetic testing for hypertrophic cardiomyopathy. Journal of Cardiovascular Translational Research. 2009;**2**:381-391

[79] Rozenfeld P, Neumann PM. Treatment of Fabry disease: Current and emerging strategies. Current Pharmaceutical Biotechnology. 2011;**12**:916-922

[80] Teekakirikul P, Kelly MA, Rehm HL, Lakdawala NK, Funke BH. Inherited cardiomyopathies: Molecular genetics and clinical genetic testing in the postgenomic era. The Journal of Molecular Diagnostics. 2013;**15**(2):158-170

[81] Biagini E, Coccolo F, Ferlito M, Perugini E, Rocchi G, Bacchi-Reggiani L, Lofiego C, Boriani G, Prandstraller D, Picchio FM, Branzi A, Rapezzi C. Dilated-hypokinetic evolution of hypertrophic cardiomyopathy: prevalence, incidence, risk factors, and prognostic implications in pediatric and adult patients. Journal of the American College of Cardiology. 2005;**46**:1543-1550

[82] Sen-Chowdhry S, Syrris P, Prasad SK, Hughes SE, Merrifield R, Ward D, Pennell DJ, McKenna WJ. Left-dominant arrhythmogenic cardiomyopathy: An under-recognized clinical entity. Journal of the American College of Cardiology. 2008;**52**:2175-2187

[83] Oechslin E, Jenni R. Left ventricular non-compaction revisited: A distinct phenotype with genetic heterogeneity? European Heart Journal. 2011;**32**:1446-1456

[84] Bos JM, Poley RN, Ny M, Tester DJ, Xu X, Vatta M, Towbin JA, Gersh BJ, Ommen SR, Ackerman MJ. Genotype-phenotype relationships involving hypertrophic cardiomyopathy-associated mutations in titin, muscle LIM protein, and telethonin. Molecular Genetics and Metabolism. 2006;**88**:78-85

[85] Zhang M, Tavora F, Burke A. Desmosomal protein gene mutations in patients with idiopathic DCM. Heart. 2011;**97**:2090

[86] Klauke B, Kossmann S, Gaertner A, Brand K, Stork I, Brodehl A, Dieding M, Walhorn V, Anselmetti D, Gerdes D, Bohms B, Schulz U, Zu Knyphausen E, Vorgerd M, Gummert J, Milting H. De novo desmin-mutation N116S is associated with arrhythmogenic right ventricular cardiomyopathy. Human Molecular Genetics. 2010;**19**:4595-4607

[87] Otten E, Asimaki A, Maass A, van Langen IM, van der Wal A, de Jonge N, van den Berg MP, Saffitz JE, Wilde AA, Jongbloed JD, van Tintelen JP. Desmin mutations as a cause of right ventricular heart failure affect the intercalated disks. Heart Rhythm. 2010;**7**:1058-1064

[88] van Tintelen JP, Van Gelder IC, Asimaki A, Suurmeijer AJ, Wiesfeld AC, Jongbloed JD, van den Wijngaard A, Kuks JB, van Spaendonck-Zwarts KY, Notermans N, Boven L, van den Heuvel F, Veenstra-Knol HE, Saffitz JE, Hofstra RM, van den Berg MP. Severe cardiac phenotype with right ventricular predominance in a large cohort of patients with a single missense mutation in the DES gene. Heart Rhythm. 2009;**6**:1574-1583

[89] Taylor M, Graw S, Sinagra G, Barnes C, Slavov D, Brun F, Pinamonti B, Salcedo EE, Sauer W, Pyxaras S, Anderson B, Simon B, Bogomolovas J, Labeit S, Granzier H, Mestroni L. Genetic variation in titin in arrhythmogenic right ventricular cardiomyopathy-overlap syndromes. Circulation. 2011;**124**:876-885

[90] Hershberger RE, Norton N, Morales A, Li D, Siegfried JD, Gonzalez-Quintana J. Coding sequence rare variants identified in MYBPC3, MYH6, TPM1, TNNC1, and TNNI3 from 312 patients with familial or idiopathic dilated cardiomyopathy. Circulation. Cardiovascular Genetics. 2010;**3**:155-161

[91] Moller DV, Andersen PS, Hedley P, Ersboll MK, Bundgaard H, Moolman-Smook J, Christiansen M, Kober L. The role of sarcomere gene mutations in patients with idiopathic dilated cardiomyopathy. European Journal of Human Genetics. 2009;**17**:1241-1249

[92] Mirza M, Robinson P, Kremneva E, Copeland O, Nikolaeva O, Watkins H, Levitsky D, Redwood C, El-Mezgueldi M, Marston S. The effect of mutations in a-tropomyosin (E40K and E54K) that cause familial dilated cardiomyopathy on the regulatory mechanism of cardiac muscle thin filaments. The Journal of Biological Chemistry. 2007;**282**: 13487-13497

[93] Venkatraman G, Harada K, Gomes AV, Kerrick WG, Potter JD. Different functional properties of troponin T mutants that cause dilated cardiomyopathy. The Journal of Biological Chemistry. 2003;**278**:41670-41676

[94] Ashrafian H, Watkins H. Reviews of translational medicine and genomics in cardiovascular disease: New disease taxonomy and therapeutic implications cardiomyopathies: therapeutics based on molec-ular phenotype. Journal of the American College of Cardiology. 2007;**49**:1251-1264

[95] Norton N, Robertson PD, Rieder MJ, Zuchner S, Rampersaud E, Martin E, Li D, Nickerson DA, Hershberger RE. Evaluating pathogenicity of rare variants from dilated cardiomyopathy in the exome era. Circulation. Cardiovascular Genetics. 2012;**5**:167-174

[96] Van Driest SL, Vasile VC, Ommen SR, Will ML, Tajik AJ, Gersh BJ, Ackerman MJ. Myosin binding protein C mutations and compound heterozygosity in hypertrophic cardiomyopathy. Journal of the American College of Cardiology. 2004;**44**:1903-1910

[97] Alders M, Jongbloed R, Deelen W, van den Wijngaard A, Doevendans P, Ten Cate F, Regitz-Zagrosek V, Vosberg HP, van Langen I, Wilde A, Dooijes D, Mannens M. The 2373insG mutation in the MYBPC3 gene is a founder mutation, which accounts for nearly one-fourth of the HCM cases in the Netherlands. European Heart Journal. 2003; **24**:1848-1853

[98] Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 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;**2014, 35**(39):2733-2779

[99] Kacem S, Cheniti G. Genetic testing in management of hypertrophic cardiomyopathy-fifth in series. European Journal of Cardiology Practice. 2015;**13**:26

[100] Maron BJ, Olivotto I. Hypertrophic cardiomyopathy. In: Mann DL, Zipes DP, Libby P, Bonow RO, Braunwald E, editors. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia: Elsevier Saunders; 2015;**66**:1574-1588