REVIEW ARTICLE

Hypertrophic Cardiomyopathy

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SUMMARY

Hypertrophic cardiomyopathy is a multigenetic cardiac disease with autosomal dominant pattern of inheritance and incomplete penetrance, with the exclusion of those cases caused by mutations in the mitochondrial genome. The disease is usually caused by mutations in several sarcomeric contractile protein genes. Mutations have been found in four genes that encode components of the thick filament: ß myosin heavy chain (5), essential myosin light chains (6), regulatory myosin light chains (6), and cardiac myosin binding protein -C (7), (8); in five genes that encode thin filament proteins: cardiac actin (9), cardiac troponin T (10), cardiac troponin C (11), cardiac troponin I (12), and α-tropomyosin (10); and in the sarcomeric cytoskeletal protein titin (13). In addition to mutations in contractile sarcomeric proteins, mutations in other genes encoding for non-sarcomeric proteins also have been identified in patients with-non pure form of hypertrophic cardiomyopathy. As a complex cardiac disease, hypertrophic cardiomyopathy has unique pathophysiological characteristics and a various morphological, functional, and clinical features.
Key words: Hypertrophic cardiomyopathy, MYH7 gene, MYBPC3 gene, TNNT2 gene

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Until the latter half of the 1980s, the accumulated knowledge of cardiomyopathies was mainly clinical and descriptive, since the causes for the vast majority of these primary myocardial diseases were unknown. Although myocardial hypertrophy and development of cardiac failure occurs commonly in these patients, the molecular basis of cardiac growth, hypertrophy, and a repair was until recently, totally elusive. Molecular biology has opened the door to a new understanding of some of these disorders (1).

Hypertrophic cardiomyopathy (HCM) is a multigenetic cardiac disease with autosomal dominant pattern of inheritance and incomplete penetrance, with the exclusion of those cases caused by mutations in the mitochondrial genome. According to Marian at al. (2) approximately two-thirds of patients have a family history of HCM. The rest of the cases are sporadic, which is due to mutations that arise *de novo*.

In these days, hypertrophic cardiomyopathy is defined as a disease of the sarcomere because majority of the genes that are associated with HCM development encode for cardiac sarcomeric proteins, however, other disease causing - genes have been found (3). This heart disease is mostly due to multiple mutations in at least sixteen genes that have been identified so far. To be able to understand how mutations in different genes especially those that encode for contractile proteins cause hypertrophic cardiomyopathy, it will be necessary to understand the functional consequences of the mutations at a molecular level. It is already known, that different mutant proteins cause similar functional abnormalities, which sequentially initialize the same disease pathways, although they are members of the same functional group and have very different properties and roles. Some of them have enzymatic and force generating roles (e.g. myosin heavy chain), while others play structural roles (e.g. myosin binding protein C) or have regulatory functions (e.g. troponins T, I and α-tropomyosin).

Mutations that cause hypertrophic cardiomyopathy can be located in one of several very large genes, and most of the affected families do not have sufficient members to allow statistically significant chromosome linkage analysis (4).

Mutations have been found in four genes that encode components of the thick filament: ß-MHC (5), essential MLC (6), regulatory MLC (6), and cMyBP-C (7), (8); in five genes that encode thin filament proteins: cardiac actin (9), cardiac troponin T (10), cardiac troponin C (11), cardiac troponin I (12), and α-tropomyosin (10); and in the sarcomeric cytoskeletal protein titin (13).

In addition to mutations in contractile sarcomeric proteins, mutations in other genes encoding for non-sarcomeric proteins also have been identified in patients with-non pure form of HCM. Mutations in the $+\gamma_2$ regulatory subunit of an AMP-activated protein kinase (AMPK, gene: PRKAG2) were found to be responsible for a variant of HCM associated with ventricular preexcitation (Wolf-Parkinson-White syndrome) at the chromosome 7q36 locus (14). Mutations in the gene encoding the cytoskeletal muscle LIM protein has also been identified (15). Thus, hypertrophic cardiomyopathy is a genetic model of cardiac hypertrophy caused by a diverse array of mutations in a variety of genes, with the pure form (no other cardiac or non-cardiac phenotype) resulting from mutations in contractile sarcomeric proteins.

For each disease gene, a variety of different mutations have been reported. Methylated CpG dinucleotides within the genome are particularly prone to point mutations (16). Alternatively, a significant number of novel genes may remain to be identified. Generally, individuals with HCM causing mutations are heterozygous, however, cases of homozygous HCM mutations have been also reported. One of these was an $Arg^{869}Gly$ point mutation in the MYH7 gene (17), and the other was a $Ser^{179}Phe$ mutation in the cardiac troponin T gene (18). Both mutations caused particularly severe phenotype with onset in childhood and premature death.

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It is not currently possible to establish a correlation between the presence of the mutation in one of the sarcomeric genes and a particular phenotype (5). Moreover, the same mutation can be found in individuals with a different clinical manifestation (19). A systematic evaluation of genotyped pedigrees found that up to 30 % of adults who carry a mutation were "healthy" with a normal echocardiography and ECG as regards conventional diagnostic criteria (20). These "healthy carriers" may however present mild abnormalities on echocardiography which may represent early expression of the disease (21).

Since the majority of HCM disease genes encode protein components of the sarcomere, it has been widely proposed that left ventricular hypertrophy is not a primary manifestation but develops as compensatory response to sarcomere dysfunction. Characterization of the fundamental deficit resulting from HCM-causing gene mutations has been a major focus of research over the last decade. A variety of techniques have been used to examine the effects of mutations on sarcomere structure and function, ranging from in vivo studies of myocardial performance in genetically engineered mouse models to in vitro studies of interactions between single actin and myosin molecules. It is clear, that the type of strategy employed to investigate the effects of sarcomere protein mutations greatly influences the outcome, with conflicting results found for the same mutation in many cases. Investigators have sought to answer questions such as whether the various sarcomere protein mutations cause similar or diverse effects on sarcomere structure and function and whether sarcomere protein mutations act by a dominant negative mechanism or alter function by causing haploinsufficiency. In the dominant negative model, both wild-type and mutant proteins are present in equivalent proportions; the mutant peptide is stably incorporated into the sarcomere but acts as a "poison polypeptide" and perturbs wild-type protein function. Alternatively, mutations may result in null alleles or cause a reduction in the amount of wild-type protein, leading to an imbalance of sarcomere protein stoichiometry. Mutations that truncate the encoded protein are thought to act by haploinsufficiency. Understanding the consequences of sarcomere protein mutations is an essential prerequisite for determining the stimulus for hypertrophy in HCM. For example, if HCM-causing mutant proteins merely induced an imbalance in the stoichiometry of the protein components involved in sarcomere assembly, in vitro analysis of the mutant proteins per se would have little merit (22).

A characteristic feature of human HCM, like many others autosomal dominant diseases, is the presence of significant variability in the phenotypic expression of phenotypes. It is now well established that genetic factors other than the causal mutations, referred to as the modifier genes, affect the phenotypic expression of a disorder such HCM. Modifier genes are neither necessary nor sufficient to cause HCM, but they affect the severity of the disease significantly. Thus far studies to identify the potential modifier genes for HCM have been limited to allelic association studies, whereby the possible association of variants of candidate genes with cardiac phenotypes has been explored. In this regard, few studies have shown that functional variants of angiotensin-1 converting enzyme (ACE-1) gene are potential modifiers of HCM phenotype, since they are associated with the risk of SCD and the magnitude of left ventricular hypertrophy. Patients with the DD genotype exhibit higher tissue and plasma levels of ACE-1, a higher incidence of sudden death, and more extensive hypertrophy than those with the II genotype. Marian and Roberts (2) have explored association of functional variants of several trophic factors and have shown that variants of endothelin-1 and tumor necrosis factor-α are also potential modulators of cardiac phenotypes in hypertrophic cardiomyopathy.

DISEASE CAUSING GENES

MYH7 gene

The ß-myosin heavy chain gene was the first gene identified as a disease causing gene in HCM. Most mutations found in this gene are related to distinct functional and structural domains of the ß-myosin heavy chain. These defects are clustered at specific regions in the globular head of the myosin molecule (sub fragment S 1), that are, firstly, associated with the actin binding site, secondly, near nucleotide binding site (ATP binding), thirdly, adjacent to the region that connects two reactive cystein residues, fourthly, at the myosin light chain binding interface, and lastly, at the head rod junction.

According to Rayment (23), many of the mutations lie at the interface between structural domains and may influence the transduction of chemical energy into movement. The mutations observed in the ß-MHC serve to indicate parts of the molecule that are important for function. They represent a class of molecules that are probably partially impaired and as such highlight the more subtle features of myosin (23).

The primary genetic defect appears to be impaired contractility, which triggers the release of growth factors that result in compensatory hypertrophy and fibroblast proliferation (24). Up regulation of growth factors has been confirmed in FHC mouse models and in humans with FHC (25).

Defects of the MYH7 gene account for the largest proportion of severe cases of HCM. Genotype - phenotype correlative studies have shown that distinct mutations in the MYH7 gene may be associated with different prognosis (26, 27, 28).

The previously reported frequency of MYH7 gene mutations in HCM has ranged from 30 to 50 % in the initial studies to 10–20 % recently (26, 13, 29).

Mutations that are associated with a high incidence of SCD and premature death often exhibit high penetrance and an early age of onset. In contrast, those associated with a benign prognosis often exhibit low penetrance, late onset of disease, and milder left ventricular hypertrophy. Homozygosity for causal mutations and compound mutations has been described that leads to a more severe morphological phenotype and a higher incidence of SCD (30). Certain mutations in the ß-myosin heavy chain gene were associated with normal life expectancy, whereas others were reported to decrease survival because of sudden arrhythmic death or heart failure (27, 31). Such gene defects in MYH7 and other HCM-causing genes have been designated in the literature as either "benign" or "malignant". It has also been suggested that charge – changing amino acid substitutions may be associated with more severe disease (27), (32). It has, however, become clear, that intrafamilial variation in also marked, particularly with regard to the morphological features of the disease.

MYBPC3 gene

The cardiac myosin binding protein C (cMyBP-C) isoform is expressed exclusively in the cardiac tissue. It is located in the sarcomere A bands and forms a series of seven to nine transverse bands spaced at 43-nm intervals. MYBPC3 is comprised of 24 kb of genomic DNA with 37 exons that encode a protein of 1, 274 amino acids.

The protein has multiple immunoglobulin C2-like and fibronectin type 3 domains, as well as a cardiac specific region, a phosphorylation region, and overlapping myosin and titin binding sites. MYBPC3 mutations are found in ~15 to 20 % individuals with HCM. Over 140 mutations have been reported. The majority of mutation represents nucleotide substitutions, insertions, dele-

tions, or splice site mutations that result in truncation of the cMyBP-C protein with loss of the myosin and titin binding sites. Missense mutations that preserve the myosin and titin binding sites have also been found. Mutations in the MYBPC3 are generally associated with a relatively mild cardiac hypertrophy and a low incidence of SCD as compared to mutations in the MYH7 gene. However, as shown by Erdmann et al. (34), malignant features such as SCD, sustained ventricular tachycardia and severe hypertrophy also occur. The primary defect caused by mutations in the MYBPC3 gene is likely to be diverse and differ for missense, frame-shift and truncation mutations. The cMyBP-C proteins carrying the missense mutations could incorporate into myofibrils but cause myocyte mechanical dysfunction and impair generation of the contractile force. Insertion/deletion mutations could lead to expression of truncated proteins that degrade immediately and cause haplo-insufficiency, or do not properly incorporate into sarcomere and cause sarcomere dysgenesis. Thus, mutations in the MYBPC3 gene could affect orderly formation of thick filaments and/or alter cardiac myocyte mechanical function, particularly in response to adrenergic stimulation.

Overall, the expected functional defect conferred by mutations in the MYBPC3 gene is impaired generation of force of contraction by the cardiac myocytes, which could lead to increased myocyte stress and subsequent activation of stress-responsive signaling kinases and increased expression of trophic and mitotic factors in the heart (24).

TNNT2 gene

Cardiac troponin T is expressed in embryonic and adult heart and in developing skeletal muscle. TNNT2 is comprised of 17 kb of genomic DNA and has 17 exons.

A number of different cardiac troponin T isoforms are produced by alternate splicing. The principal isoform in the adult heart consists of 288 amino acids and has two major domains: an NH_2- terminal domain that interacts with tropomyosin and a COOH-terminal domain that binds to tropomyosin, troponin C, and troponin I.

TNNT2 mutations account for ~5 to 10 % of cases of hypertrophic cardiomyopathy.

CONCLUSION

As described above, genetic heterogeneity (i.e. multiple different genes causing a similar phenotype) has been identified in hypertrophic cardiomyopathy. Similar genetic heterogeneity has been reported for dilatated cardiomyopathy, as well. However, it appears that there is a commonality of the proteins that are mutated in each disease. This leads to propose the „final common pathway“ hypothesis, which states that hereditary cardiovascular diseases with similar phenotypes and genetic heterogeneity will occur due to abnormalities in genes encoding proteins of similar function or genes encoding proteins participating in a common pathway cascade (34). The relevance of the hypothesis is its ability to classify disease entities on a molecular and mechanistic basis, i.e. „sarcomyopathies“, or „cytoskeletopathies“ for hypertrophic cardiomyopathy and dilatated cardiomyopathy, respectively, which could lead to more focused approaches to gene discovery and future therapeutic interventions (35).

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COMMENTARY

Čapek P., Brdička R.: "Hypertrophic cardiomyopathy – review article."

Contribution of genetics to the diagnosis and treatment of hypertrophic cardiomyopathy from the clinical cardiologist's perspective.

Hypertrophic cardiomyopathy (HCM) is a genetically induced disease. It is known that more than 200 causal mutations lead to the enormous variability of clinical symptoms of this disease. The most important known mutations are described in the paper "Hypertrophic cardiomyopathy" by Čapek and Brdička. The subject matter described here makes interesting reading, though it is slightly abstract for a cardiologist, even if it closely concerns his or her own patients – and all the more so if the clinical practice specialises in patients with HCM.

The crucial question in practice is whether the very extensive genetic research of HCM also has some subsequent clinical implications. There is no simple answer to the question put in this manner. Studies dealing with correlations between genotype and phenotype have not produced any positive result in the sense of formulation of clinical algorithms determined by the genotype of individual patient. Clinical symptoms of this disease can vary considerably within a family or even between identical twins. There is also a definite variability within the frame of one and the same mutation. Today this variability is seen in the context of 1) the function of other modifying genes or polymorphisms (there is probably a certain "genetic cocktail" determining phenotype changes) and 2) the influence of external environment. Thus it is very difficult to ascertain whether a specific mutation will have a "benign" or "malignant" character and, based on this verdict, to stratify the individual risk and optimise the therapy. In other words, the genetics have come to stagnate in the aforementioned sense because of the wide genotype heterogeneity and also subsequent clinical symptoms. It is not possible to indicate the most viable means of preventing sudden death (i.e. the implantation of cardioverter defibrillator) on the basis of genotype determination. Grouping of mutations not on the basis of certain individual genotype but according to the concrete effect and functional consequences of mutation could be a solution for stratification of risk on the basis of genetic test. It seems that the extent of functional changes at the sarcomeric level could be of most significance from the whole functional string beginning with genotype, proceeding with concrete modified proteins, changes on the level of sarcomere, myocardium and the whole heart for further research (1).

To further complicate the situation it appears that the cause of HCM is not necessarily only the mutation undermining changes of proteins at the level of sarcomere. The so-called non-sarcomeric mutations are also relevant. They undermine changes of cytoskeletal proteins responsible for localisation and organization of intracellular sarcomeres. They are functionally connected with sarcomeres and therefore it

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is not surprising that they can lead to the development of disease with the same characteristics as the classic "sarcomeric HCM". Moreover, the disease induced by autosomal dominant mutation of γ2 regulating subunit (PRKAG2) of AMP-dependent protein kinase is still further from standard diagnosis of HCM. These mutation leads to the affection of cell energy metabolism and finally to glycogen accumulation connected with myocardial hypertrophy that cannot be clinically distinguished from HCM. Moreover, affected people suffer from conduction disturbances and WPW syndrome.

It seems to me that owing to the aforementioned facts, the known classification will be surpassed in the near future. Our slightly outmoded determining of diagnosis based on the presence of hypertrophy will be replaced by more precise genetic diagnosis going hand in hand with imaging methods and clinical symptoms of the disease (2). Thus, bearing in mind the considerable defects in our current knowledge, I would try to answer the question posed concerning the clinical position of genetics in diagnosis and treatment of HCM. Genetics and molecular biology has no substantial and direct significance for current diagnostic and therapeutic algorithms. On the other hand, it specifies our knowledge about the principle of the disease or diseases that we uniformly call HCM. As soon as we get more information from genetic research into HCM the first meaningful diagnostic and therapeutic methods based on the genetic tests will appear. In the meanwhile we must base our clinical strategy (based mainly on stratification of risk of sudden death) on known and verified clinical factors such as family history, incidence of syncope, malignant arrhythmias, massive left ventricular hypertrophy, inability to increase blood pressure at stress, symptoms of heart failure or presence of intraventricular obstruction.

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