

Review Article

Hypertrophic Cardiomyopathy: The Molecular Genetics

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Abstract:

Hypertrophic Cardiomyopathy (HCM) is the common monogenic form familial pathological cardiac hypertrophy. HCM is an important cause of sudden cardiac death in the young adult and a major cause of morbidity in the elderly. We discuss here the molecular genetics and recent advances in the molecular genetics of HCM. HCM became the first cardiac disease for which a molecular genetic mechanism was identified. More than 100 mutations in nine genes, that encoding sarcomeric proteins have been identified in patients with HCM, which had led to the belief that HCM is a disease of contractile sarcomeric proteins of the cardiac muscle. Approximately two-thirds of all HCM cases are caused by the mutation of the myosin heavy chain (MyHC), cardiac troponin T (cTnT) and myosin binding protein-C (MyBP-C). Genotype-phenotype correlation studies suggest that mutations in the MyHC gene are associated with more extensive hypertrophy and a higher risk of SCD as compared to mutations in genes coding for other sarcomeric proteins, such as MyBP-C and cTnT. However, there is a noteworthy variability and factors, such as modifier genes and probably the environmental factors affect the phenotypic expression of HCM. The results of different functional studies suggest that in spite of the variety of the mutations, the initial defects in HCM is abnormal cardiac myocyte function. In this era of genetics and upcoming future of precision medicine, good knowledge of its molecular basis of any disease is crucial for patient management, and HCM is not different.

Key words: Cardiomyopathy, Genetics, Pathogenesis, Mutation.

Introduction:

Sixty years ago Dr. Robert Donalds Teare, a pathologist of St. George Hospital in London first accounted for hypertrophic cardiomyopathy (HCM)¹⁻². HCM is primarily a cardiac disease that is one of the most common forms of heritable cardiac diseases³⁻⁴. HCM is the most common monogenetic disorder with a prevalence of 0.2% irrespective of gender, race or

ethnicity⁵⁻⁷. HCM results in thickening of the myocardial wall and is almost always inherited as an autosomal dominant trait caused by point mutations in structural proteins within the contractile apparatus of cardiac myocytes⁸. In HCM myocardial changes are characterized by the presence of excessive ventricular hypertrophy in the absence of conditions causing physiologic hypertrophy such as hypertension, valvular aortic stenosis, or the athletic heart⁹⁻¹⁰. HCM patients may remain asymptomatic for a very long time but may also present with varieties of clinical presentations like dyspnea, angina, palpitation, syncope and sometimes sudden cardiac death (SCD) may be the first presenting symptom¹¹⁻¹³. It is a prominent cause of sudden cardiac death in young adults^{11,14}.

Genetics of HCM:

HCM became the first cardiac disease for which a molecular genetic mechanism was identified¹⁵. It has been noted that 55 to 70% of the HCM is caused as a consequence of genetic mutations¹⁶. The most common genetic mutation has been identified as responsible for HCM are found within thirteen genes¹⁷. Mutations have been identified in patients with HCM in ten genes that encode for contractile sarcomeric proteins, two genes that code for non-sarcomeric proteins and one in the mitochondrial genome¹⁸.

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The discovery of a missense mutation in the *MYH7* gene, which encodes the β -myosin heavy chain, about two decades ago, provided the first evidence to the molecular genetic basis of HCM¹². HCM is a disease of the sarcomere and contractile elements of the myocardium. It is now recognized that HCM is a disease which is autosomal dominant in inheritance, caused by a mutation in the genes for sarcomeric proteins, resulting in myocyte disarray and hypertrophy, with or without fibrosis and small vessels abnormality. Subsequent discoveries of other sarcomeric protein abnormalities, like α -tropomyosin gene (*TPM1*), cardiac troponin T (*TNNT2*), troponin I, myosin binding protein C (*MYBPC*), essential myosin light chain, cardiac actin, titin, cardiac α -myosin, and troponin C, lead to the concept that HCM is disease of the sarcomere¹⁸. It is proposed that the sarcomeric mutation reduces the myocardial contractility, which in turn leads to increased cellular stress. Stressed myocytes produce trophic and mitotic factors that ultimately cause the myocardial changes. It is seen that *MYH7* and *TNNT2* mutation reduces the contractility of the myocytes. *TNNT2* gene mutation is thought to alter cross-bridge kinetic, thereby limiting the shortening velocity of the cardiac myocyte and increase the energetic cost of contraction¹⁸. However, the *TPM1* mutation may also show enhanced cardiac output and filamentous motility in the submaximal concentration of calcium ion. Both the active and passive phases of the diastole are abnormal in HCM.

Genes and mutations associated with HCM:

During the last three decades, genetic cause for many cardiovascular diseases has been identified and HCM is most important of them¹⁹. More than 100 different mutations in the genes that code for sarcomeric contractile proteins have been identified in patients with HCM²⁰ (Table I). HCM is often presented with triple-repeat syndromes for which several causal mutations have been identified¹⁹. Collectively these data suggest that in HCM, hypertrophy of the myocardium in spite of not having increased external load can occur as a result of mutations in various genes. Though hypertrophy is a common response of the myocardium to all sorts of stress and injury, however, hypertrophy may occur due to mutations in the non-sarcomeric proteins coding genes that are often presented with other cardiac and non-cardiac phenotypes.

Dr. Seidman mapped the first responsible gene for HCM, *MYH7* on chromosome 14q1²⁰. Subsequent screening of this gene led to the identification of the R403Q missense mutation, which is the most commonly described mutation in HCM²¹. The *MYH7* gene is comprised of 40 exons and codes for a 6 kb mRNA and a 220 kD protein²². It is the predominant

myosin isoform comprising >90% of the total myosin in the human ventricles²³. Mutations in the *MYH7* gene are the most common cause of HCM and responsible for 35-50% of all HCM cases²⁴. More than 60 different mutations of this gene have been accounted, and most of them are missense mutations. Hotspot for mutation of *MYH7* gene is located in the codons 403 and 71925-26. Two small (E930 and G10) and one large (exon 40 and 3' untranslated region) deletion and one insertion/deletion (changing AA 395-404) mutations in the *MYH7* gene have been described¹⁷⁻²⁹.

Table I: Genes responsible for HCM, their loci, and estimated frequencies of their mutations found in heritable HCM

Gene	Symbol	Locus	Frequency	Mutations
β -Myosin heavy chain	<i>MYH7</i>	14q12	~30%	67; mostly missense, a few nonsense, and 3 deletion
Myosin binding protein-C	<i>MYBPC</i>	11p11.2	~20%	29; 11 missense/nonsense, 10 splice, 8 deletion/insertion
Cardiac troponin T	<i>TNNT2</i>	1q32	~20%	14; 12 missense, 1 splice and 1 deletion
α -Tropomyosin	<i>TPM1</i>	15q22.1	~5%	4 missense mutations
Cardiac troponin I	<i>TNNT3</i>	19p13.2	~5%	7 missense and 1 deletion mutations
Myosin light chain	<i>MYL3</i>	3p21.3	<5%	2 missense mutations
Myosin light chain	<i>MYL2</i>	12q23	<5%	7 missense and 1 truncation mutations
α cardiac actin	<i>ACTC</i>	11q	<5%	2 missense mutations
Titin	<i>TTN</i>	2q24.1	<5%	1 missense mutation
α -Myosin heavy chain	<i>MYH6</i>	14q	Rare	1 missense and 1 rearrangement mutations
K voltage-gated channel	<i>KCNQ4</i>	1p34	Rare	1 deletion mutation in conjunction with deafness
Protein kinase A	<i>PRKAG2</i>	7q22	Rare	1 point mutation in conjunction with WPW
Mitochondrial DNA	<i>MTTI</i>	-	Rare	tRNA isoleucine and tRNA glycine

The second most common gene responsible for human HCM is the myosin binding protein-C (*MYBPC*) gene, which is located on chromosome 11q1130. *MYBPC* gene mutations are responsible for about 20% to 25% of all HCM cases³¹. This gene is comprised of 35 exons that span approximately 23 kb of DNA on the chromosome³⁰. More than 29 different mutations of *MYBPC* comprised of missense, deletion, and splice junction mutations have been identified³⁰⁻³³. These mutations commonly affect the splice junctions and the binding sites for MyHC and titin proteins.

The third most common gene responsible for HCM is the *TNNT2* that code for the cardiac troponin T (*TNNT2*), which account for approximately 20% of all HCM cases²⁴. It is located on chromosome 1q3 and through alternative splicing, encodes several isoforms in the heart³⁴. More than 20 mutations in the *TNNT2* gene have been identified and codon 92 is considered a hot spot for the mutation³⁵⁻³⁶. The majority of the mutations in *TNNT2* are missense and deletion mutations that involve the splice donor sites and lead to truncated proteins³⁴. Overall, mutations in the three most common genes responsible for HCM, namely the *MYH7*, *MYBPC*, and *TNNT2*, account for approximately three-fourths of all HCM cases.

Identification of mutations in the contractile sarcomeric proteins led to the conception that HCM is a disease of contractile sarcomeric proteins. Systematic screening of HCM cases for mutations in genes encoding for other sarcomeric proteins led to identification of mutations in α -tropomyosin (*TPMI*),^{35,37} cardiac troponin I (*TNNT3*),³⁸⁻³⁹ essential and regulatory light chains (*MYL2* and *MYL3*)⁴⁰, a cardiac actin (*ACTC*)⁴¹, and titin⁴². Overall, the frequencies of these mutations are relatively low and each of the above genes accounts for <5% of all HCM cases.

In addition to mutations in contractile sarcomeric proteins, mutations in two genes encoding for non-sarcomeric proteins also have been identified in patients with HCM. Recently, a deletion mutation in a potassium voltage-gated channel, *KCNQ4* located on chromosome 1p34, in a family with congenital deafness and HCM was described¹⁷. More recently, a point mutation in the AMP-activated gamma 2 non-catalytic subunit of protein kinase A (*PARAG2*) located on chromosome 7q22-q23 was described in two families with HCM and Wolff-Parkinson-White syndrome⁴³. Furthermore, mutations in mitochondrial genes encoding for tRNA isoleucine and tRNA glycine also have been associated with HCM⁴⁴. Thus, HCM 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 noncardiac phenotype) resulting from mutations in contractile sarcomeric proteins.

Molecular pathogenesis of HCM:

It is evident from in vivo and in vitro studies that the mutations in the genes responsible for HCM lead to the impaired contractile performance of the cardiac myocyte. The phenotype of sarcomeric disarray, hypertrophy and increased fibrosis are secondary to the primary defect of impaired contractile performance. To compensate for the contractile impairment, stress-responsive growth factors are released, which subsequently stimulate myocyte hypertrophy and fibroblast proliferation.

Approximately one-third of the myofibrillar proteins are the b-myosin protein, the motor unit of the sarcomere. It has a globular head that contains actin and ATP binding domains. Numerous myosin molecules assemble to form the sarcomeric thick filament⁴⁵. *MYBPC* is another thick filament that binds to myosin in the A band region of the sarcomere⁴⁶. It is also attached with the titin. Binding of MyBP-C to myosin and titin provides further stability to the structure of the sarcomere⁴⁷. Thin filaments, comprised of actin and troponin-tropomyosin complex, are involved in the generation force, as well as in the transmission of the force to cell boundaries. Cardiac troponin T, α -tropomyosin, and troponin I, each comprises <5% of the total myofibrillar protein. Troponin complex plays a major role in the Ca^{2+} regulation of cardiac contraction and relaxation⁴⁸.

Mutations in the sarcomeric genes cause structural changes that affect the sarcomere and myofibril formations. Several studies have revealed that the majority of the mutant sarcomeric proteins incorporate into myofibrils and sarcomeres⁴⁹⁻⁵⁰. Incorporation of mutation affected sarcomeric proteins into sarcomere varies according to the mutation and is reduced for a truncated mutation in the MyBP-C⁵¹. However, when these abnormal proteins are incorporated at high levels, they may induce sarcomere dysgenesis and myofibrillar disarray⁵¹⁻⁵². The globular head region of b-MyHC contains a catalytic site for ATP hydrolysis that hydrolyzes ATP to ADP and inorganic phosphate. This function is markedly reduced as a consequence of mutations in MyHC and other sarcomeric proteins⁵³.

Repeated interaction of MyHC and actin is facilitated by binding and release of Ca^{+2} . Mutations in sarcomere proteins could affect Ca^{+2} sensitivity and thus affect the interaction between actin and myosin filaments during the cardiac cycles. Though many studies show an enhanced Ca^{+2} sensitivity is imparted by the mutant of the sarcomeric proteins, the results remain controversial as they varied according to the experimental conditions⁵⁴⁻⁵⁵. However the mutation-specific increase in Ca^{+2} sensitivity of contractile elements in cardiac myocytes could play a major role in

inducing cardiac specific phenotypes in HCM. Mutations in the b-MYHC impair the ability of the affected myosin protein to displace thin actin filaments. Mutations associated with a poor prognosis shows distinct effect than those associated with a benign prognosis⁵⁶⁻⁵⁷. The mutant myosin shows impaired ability to displace actin filaments that reflects its reduced binding affinity for the actin filaments. Likewise, the interaction between the thin and thick filaments is also compromised in mutant *MYH7*⁵⁸.

Though the HCM is defined as the cardiac hypertrophy in the absence of increased external load, it is often a late manifestation of the disease and it is frequently absent in a significant number of patients having the causal mutation in the sarcomeric and non-sarcomeric genes that were mentioned earlier. Cardiac hypertrophy is the response of the myocardium to all forms of stress and injury. It is suggested that the hypertrophy in HCM is compensatory to the triggering stimulus usually provided by the abnormal contractile sarcomeric proteins produced as a consequence of mutations in the causal genes⁵⁹.

Conclusion:

HCM is a worldwide cardiovascular disease. From its first description by teare to our current body of knowledge has rapidly advanced. Genetic variants, molecular mechanisms, and clinical phenotypes of HCM vary on a patient-by-patient basis. In summary, mutations in ten contractile sarcomeric genes, two non-sarcomeric genes, and mitochondrial DNA is associated with the pathogenesis of HCM. The results of different functional studies suggest that in spite of the variety of the mutations, the initial defects in HCM is abnormal cardiac myocyte function. In this era of genetics and upcoming future of precision medicine, good knowledge of its molecular basis of any disease is crucial for patient management, and HCM is not different. In this article, we shed some lights on the molecular genetic basis of the HCM.

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