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Genotypic and Phenotypic Correlation Regarding Expression Level of Myosin Heavy Chain (Myh7) Gene Polymorphisms in Hypertrophic Cardiomyopathy

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ABSTRACT

Hypertrophic cardiomyopathy (HCM), where it can be seen as unexplained left ventricular hypertrophy, is the most common inherited cardiac disorder. This condition is a major cause of sudden death. The clinical phenotype is heterogeneous, and mutations in a number of sarcomeric contractile protein genes are responsible for causing HCM, which is usually inherited as an autosomal dominant trait. The mode of inheritance can differ from those of HCM caused by mutations in sarcomere genes. Detailed clinical evaluation and mutation analysis are, therefore, important in providing an accurate diagnosis in order to enable genetic counseling, prognostic evaluation and appropriate clinical management. This Review summarizes current knowledge on the genetics regarding beta myosin heavy chain gene (MYH7), disease mechanisms, and correlations between phenotype and genotype in patients with HCM.

KEYWORDS: Hypertrophic cardiomyopathy, MYH7, Mutations, Phenotype, Genotype

INTRODUCTION

The HCM patients show abnormally large and misaligned myocytes with increased fibrosis (Granger et al., 2011). The thickened and stiffed ventricles reduce the compliance of the heart muscle and thereby decreases preload which contributes to diastolic heart failure (Edwards et al., 2013). HCM is the most common cause of sudden cardiac death at a young age and a major cause of morbidity and mortality in the elderly. The current annual frequencies of HCM-related sudden death (SCD) area approximately 1–2% in children and adolescents, and 0.5–1% in adults (Elliott et al., 2006). Clinical presentation typically includes chest pain, exertion-related dyspnea, or impaired consciousness (Maron et al., 1996). From the genetic point of view, HCM has a predominant autosomal dominant pattern of inheritance and has complete penetrance.

In this review we examine the genetics related to MYH7 gene polymorphism which leads to HCM and the phenotype and genotype correlations regarding the MYH7 gene polymorphism.

Hypertrophic cardiomyopathy (HCM)

Cardiomyopathies are highly heterogeneous both clinically and genetically (Elliot et al., 2006) (Maron et al., 2006). Cardiomyopathies are present in all populations, with different ethnicities, age, and gender affecting disease severity and expression (Perkins et al., 2015). Although the typifying of cardiomyopathies is clearly differentiated, the clinical presentation of end stage cardiomyopathy can overlap significantly (Kraker et al., 2016).

From the genetic point of view, HCM is mostly a congenital cardiac disease. Mutations in the genes encoding the cardiac sarcomeric proteins, cytoskeletal proteins and nuclear envelope proteins are associated with HCM. HCM is mainly attributed to multiple mutations, approximately in 16 genes (Elliot et al., 2006).

Prevalence of HCM

Hypertrophic cardiomyopathy (HCM) is one of the most common genetic heart diseases with a prevalence of up to 1 in 200 people (Semsarian et al., 2015). South Asian populations have one of the highest rates of cardiovascular disease (Dhandapany et al., 2009). South Asian populations with large ethnic diversity, potentially carries region-specific polymorphisms. The variability in disease penetrance and phenotypic expression of variants associated with HCM is high.

Diagnosis of HCM

In adults, HCM is defined by left ventricular myocardial wall thickness more than ≥15 mm in one or more segments (Rickers et al., 2005). Genetic and non-genetic disorders can present with lesser wall thickening (13–14 mm). Therefore family history, non-cardiac symptoms and signs, electrocardiogram (ECG) abnormalities and laboratory tests are used in diagnosis of HCM (Rickers et al., 2005). In genetic forms of HCM, mutation carriers can have non diagnostic morphological abnormalities which are associated with abnormal ECG findings (Gersh et al., 2011). Age is one of the most important factors when considering the possible causes for HCM (Hundley et al., 2010). Looking into three to four generation family pedigree helps to confirm a genetic origin of disease and identifies other family members that are at risk of disease development (Rickers et al., 2005).

Pathophysiology of HCM

HCM leads to hypertrophy of the left ventricle with or without the presence of LV outflow tract (LVOT) obstruction (Grover et al., 1989). HCM can also be broadly classified based on the location of hypertrophy, with examples such as the proximal septum or the apex (Parag and Harry, 2014). Cardiac contractility is decreased in hypertrophic cardiomyopathy (HCM) and that the preserved or increased ejection fraction observed in patients with HCM is a result of the concentric nature of the hypertrophy (Ostman and Wettrell, 2000). The majority of mutation in HCM are missense mutations and do not appear to interfere with initial assembly and the proper alignment of myofilaments and sarcomeres. Therefore, proteins with missense mutations exert a dominant-negative effect on myocyte function following incorporation into myofibrils (Marian et al., 2001).

Genetic influence on HCM

According to most studies, approximately 50% of the HCM cases would have mutations in the genes encoding the cardiac myosin-binding protein C3 (MYBPC3) or the cardiac heavy chain myosin (MYH7). Mutations in MYH7 would be more frequent in severe forms of hypertrophy and in patients with a family history of HCM or sudden cardiac death.

The mutations associated with HCM can be seen in both thick filament proteins (MYH7, MYBPC3) and thin filament proteins (CTT, CTC, CT1 and α troponin).

Nine sarcomeric genes carry the majority of HCM-related mutations and the encoded proteins are β-myosin heavy chain (MYH7), cardiac myosin binding protein C (MYBPC3), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), α-tropomyosin (TPM1), regulatory myosin light chain (MYL2), essential myosin light chain (MYL3), cardiac α-actin (ACTC), and cardiac troponin C (TNNC1) (Marsiglia et al., 2013).

In addition another group of mutations have been reported in the genes encoding sarcomeric Z-disc proteins such as muscle LIM protein, α-actinin, or telethonin (Edwards et al., 2013). The number of studies focusing on HCM-associated mutations in South Asia is disproportionately small when considering the size of this population and collective increased risk of CVD. To date, only 21 of the published variants associated with HCM have been documented in South Asia (Kraker et al., 2016). In the case of HCM, over 80% of known HCM associated mutations occur in MYBPC3 and MYH7 alone, while an additional 10% come from TNNT2 and TNNI3 (Perkins et al., 2015). Thus, at least 90% of known HCM cases originate from four sarcomeric genes.

Mutations in MYH7 gene

Dr. Seidman and her group mapped the first locus to chromosome 14q1 and identified the R403Q missense mutation in the β-MyHC as the first causal mutation for HCM (Geisterfer et al., 1990). MYH7 is the most common geneticpathological gene of HCM (Ackerman et al., 2011). MYH7 mutations are found in nearly 20% of HCM patients (Coto et al., 2012). In some articles it says that β-MyHC gene is accounting for approximately 35–50% of all HCM cases (Marian et al., 2001). MYH7 comprises of 40 exons and codes for a 6 kb mRNA and a 220kD protein. Codons 403 and 719 are considered hot spots for mutations. The majority of the mutations are located in the globular head of the myosin molecule. The frequency of each particular MYH7 mutation is relatively low (Marian et al., 2001).

The complete nucleotide sequence of MYH7 has already been published (Hershberger et al., 2008). MYH7 related cardiac diseases are more frequent (Tajsharghi et al., 2003) and include familial hypertrophy.

The studies regarding the correlations between genotypes for different mutations and their associated phenotypes are limited (Hermida et al., 2004).

MYH7 is divided into three regions: the subfragment 1 (S1), subfragment 2 (S2) and light meromyosin (LMM) (Martynovich et al., 2015).

MYH7 encodes cardiac b-myosin heavy chain (b-MHC), which is the major part of the thick filament of the sarcomere. Missense mutations in the globular head domain of b-MHC tend to produce HCM because they prevent interaction with actin, which is necessary for proper sarcomeric contraction (Kraker et al., 2016). 289 mutations have been found in MYH7 that are thought to produce HCM, and this gene comprises 40% of the genetic profile of the disease. Only eight of these variants have been published in South Asia. Mutations in MYH7 are associated with early-onset and extensive left ventricular hypertrophy (LVH) and clinically are associated with an increased risk of atrial fibrillation, SCD and heart failure. Due to its clinical severity, the MYH7-R403Q variant was the first HCM-causing mutation to be discovered (Kraker et al., 2016).

Since most of the single-nucleotide polymorphisms (SNPs) mutations have been reported in this gene. Common genetic variations are in exons 7, 12, 19, 20 and 23 of this gene were found in HCM, which emphasizes the role of genetic modifiers (Tajsharghi et al., 2003). High mutation clustering within those regions was reported by many scientists (Tajsharghi et al., 2003).

Mattos et al, found that from six families with HCM caused by the MYH7 gene, 55% were phenotype-positive. In the phenotype-positive individuals, the maximal wall thickness varied from 13 to 26 mm (mean of 20 ± 4 mm). The p.Glu1468Lys mutation, identified in three families, had not been previously reported in the literature. Nevertheless, all bioinformatic tools favored its pathogenic potential. Analysis of cosegregation showed that all family members affected were also carriers of mutations, except for one, who was considered normal (Mattos et al., 2016).

In a study conducted by Villanueva et al, the MYH7 gene mutation was present in 33 patients (57.8%/n=). Myocardial dysfunction was rare in this study, with only two patients presenting LV dysfunction (40% and 45%). The left ventricular wall thickness of HCM patients with mutations in MYH7 gene was 25.1 ± 1.24mm (normal <15mm) (Villanueva et al., 2015).

Eliecer et al revealed that internal intronic mutations that affected splicing were also present in these genes in some HCM patients. The full sequencing of these genes with massive next-generation sequencing would help to elucidate the full mutational spectrum of sarcomeric genes in HCM (Coco et al., 2012)

Genotype phenotype correlation studies

At the molecular level, the complexity of HCM is underlined by numerous genes that are expressed in any cell of the cardiovascular system (Kontaraki et al., 2007). Quantitative real time reverse transcriptation PCR is an effective tool for identifying a subset of these genes that are related to cardiovascular diseases (Kontaraki et al., 2007), (Epstein et al., 1992). Genotype, phenotype correlation studies suggest that the mutations in the causal genes, such as the MYH7, TNNT2, and MYBPC3, affect the phenotypic expression of HCM, particularly the magnitude of cardiac hypertrophy and the risk of SCD (Marian, 2002). Mutations in the β-myosin heavy chain are generally associated with an early onset of disease, more extensive hypertrophy, and a higher incidence of SCD (Marian, 2002). Mutations in MYBPC3 gene are often associated with a low penetrance, mild hypertrophy, and a low incidence of SCD (Marian, 2002).

A study by Weissler et al. showed lack of phenotypic differences between MYH7 and MYBPC3 associated hypertrophic cardiomyopathy when assessed by cardiac magnetic resonance imaging (CMR) (Weissler et al., 2017)

A study by Moolman et al, described a novel MYH7 mutation, resulting in the substitution of a threonine (T) residue for an alanine (A) residue at codon 797 (A797T), in two South African HCM patients which leads to SCD (Moolman et al., 2000)

MYH7 encodes the MHC-b isoform mainly expressed in cardiac muscle. It is the commonest gene associated with HCM. MYH7-H1717Q is a novel missense mutation and results in a histidine-to-glutamine substitution p.H1717Q in MHC-b. MYH7-H1717Q had HCM pathogenic effects and is therefore proposed to be a disease-causing mutation in this family (wang et al., 2016).

In addition, a study by Derdaet al, describes a connection of the most common gene mutations in HCM with alterations of circulating miRNA levels. Results of this study suggest that there could be an inter-relation between MYH7 gene mutation and miR-29a levels. Also a link between miRNAs and a mutation in the MYH7 gene has already been shown in tissues of patients with HCM (Derda et al., 2015).

TheArg403Gln and Arg453Cys mutations cause severe disease with high penetrance (~100%), severe hypertrophy, and high rates of sudden death and other disease-related complications. By contrast, the Val606Met mutation in the same gene is associated with moderate LVH but good prognosis. Not all families with MYH7 mutations have high penetrance and moderate to severe hypertrophy (Keren et al., 2006).

DNA microarray analysis is an efficient method of myocardial and vascular tissue expression analysis in cardiovascular diseases (Nanni et al., 2006).

Most of the expression studies have been done using myocardial tissue samples. The sample size of those studies was very low and most of the studies were done using the cells of laboratory animals' other than human cardiomyocytes. A study by Kai et al. with the use of myocardial biopsy samples, in HCM patients with MYH7 mutation showed greater cellular hypertrophy. The study group consisted of 17 HCM patients and 7 controls (kai et al., 1998).

A study using frozen surgical myectomy specimens from 47 patients with HCM which were examined and genotyped for mutations involving 8 myofilament-encoding genes by The is et al. Overall, 25 of 47 (53%) patients had myofilament-HCM, including 12 with MYBPC3-HCM and 9 with MYH7-HCM (Theis et al., 2009).

Another method of performing an expression study is by using a high throughput gene expression platform based on microfluidic dynamic arrays. Similar results are obtained when conventional RT-qPCR data from microliter volume samples obtained with cDNA was compared to the microarray data (Spurgeon et al., 2008). Altered gene expression patterns assessed by microarray methodology have been demonstrated in the diseased human heart (Seo et al., 2006).

However, gene expression studies from human hearts, especially in conditions that are not end stage, are frequently

hindered from a paucity of tissue samples available. Therefore, there is a need to explore tissues other than the myocardium for potential diagnostic precision in heart disease (Kontakari et al., 2007). Gene expression profiling from blood RNA may hold promise in this regard. Blood RNA gene expression profiling provides a basis for the detection of infectious and other diseases, and it has also become evident that blood cells can also provide usable genomic information for cardiovascular conditions (Kontakari et al., 2007).Therefore, it is challenging to investigate gene expression in blood samples, instead of cardiac tissues, as a potential surrogate marker for the type and severity of heart disease.

In the study by, Kontaraki et al. real-time RT-PCR on human blood samples has been used to quantify various transcripts of genes that are important for heart development, which are known to be implicated in heart hypertrophy as MYH7.

The expression of MYH7, has been studied in PBMCs of patients with HCM (n=30) compared to healthy control individuals (n=20). Real-time RT-PCR has shown a markedly increased expression of MYH7 in circulating PBMCs and MYH7 level has been found higher, compared to controls (Kontakari et al., 2007).

There was a significant correlation between MYH7 (r=.45, Pb.01) gene expression and LVM in patients with HCM. These results define a positive contribution of MYH7 gene expression to the development of left ventricular hypertrophy. Primer sequence used for Q RT-PCR in MYH7 gene expression study was F: 5V-AAAAAGACTTTGAGCTGAATGCT-3V and R: 5V-CAGCTTCTCCACC TTAGCC-3V, which contain 161 base pairs (NM_000257).

More than 100 genes that are significantly up-regulated or down-regulated in patients with coronary disease compared with the normal control subjects have been identified in a study performed using PBMCs. Although this was a small study, it points to the feasibility of using gene expression profiling of blood to detect coronary heart disease. Another recent study also provides additional evidence that blood gene expression profiling might have utility in the detection of atherosclerosis. However, it provides proof on concept that blood-based gene expression data is informative for an individual's overall inflammatory state, with possibly more specific information relevant to carotid atherosclerosis. Significant progress has been made in the application of genomic information to predict the risk of acute rejection in patients who have undergone cardiac transplantation by using PBMCs in analysis of gene expression (Seo et al., 2006).

A study by Zhao et al. revealed that deconvolution of gene expression profiles for heterogeneous samples can be performed accurately when sufficiently accurate estimates of the proportional representation of component cell types in each sample are available and when expression profiles of the components are sufficiently different (Zhao et al., 2010).

Another example of performing gene expression using blood was a study by Damas et al. which revealed that enhanced expression of chemokines (MIP-1α, MIP-1β and IL-8)and the gene expression of their corresponding receptors (CC chemokine receptor [CCR] 1, CCR5, CXC chemokine receptor [CXCR] 1 and CXCR2) are also significantly increased in mono nuclear cells from patients with CHF . In addition, CCR2 (i.e., the MCP-1 receptor) and CX3CR (the fractalkine receptor) showed enhanced gene expression in CHF (Damas et al., 2001).

Mutations in the β-MyHC are associated with onset of HCM, more extensive hypertrophy, and a higher incidence of SCD than others (Marian et al., 2001).

CONCLUSION

HCM is a common inherited cardiac disease with remarkable clinical and genetic heterogeneity.

Mutations in MYH7 gene are responsible for the disease in most cases, but mutations in other genes have also been implicated. Molecular genetic testing can benefit patients by facilitating accurate diagnosis and identifying gene-positive or gene-negative individuals. The identification of the disease causing mutations in MYH7 gene could be used as a clinical tool for prediction of disease severity and risk stratification for SCD. However, above findings demonstrate that currently available genetic testing, which includes MYH7 and other genes known to cause HCM, may provide additional clinical information.

However, gene expression studies from human hearts, especially in conditions that are not end stage such as hypertrophic cardiomyopathy (HCM), can be performed using blood RNA other than using cardiac tissue samples. Gene expression profiling from blood RNA may hold promise in this regard. Blood RNA gene expression profiling provides a basis for the detection of infectious and other diseases and it has also become evident that blood cells can also provide usable genomic information for cardiovascular conditions. Therefore, it is challenging to investigate gene expression in blood samples, instead of cardiac tissues, as a potential surrogate marker for the type and/or severity of heart disease. It is revealed that the molecular pathways leading from genotype to phenotype are not fully understood (Yang et al., 2015). However the changes in the expression of regulatory long non coding RNAs in HCM have not yet been reported (Yang et al., 2015)

Thus, extensive studies are required to discover pathogenicity and the physiological mechanisms of these variants. Furthermore, studies are needed to find the contribution of modifier genes and environmental factors to disease phenotypes. Conducting genotype-phenotype correlation studies will lead to improve understanding of

HCM and, consequently, improved treatment and management options for this high-risk population.

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