Published in final edited form as:

Curr Opin Cardiol. 2002 May ; 17(3): 242–252. doi:10.1097/01.HCO.0000013803.40803.6A.

Modifier genes for hypertrophic cardiomyopathy

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Abstract

During the past decade, more than 100 mutations in 11 causal gene coding for sarcomeric proteins, the γ subunit of AMP-activated protein kinase and triplet-repeat syndromes and in mitochondrial DNA, have been identified in patients with hypertrophic cardiomyopathy (HCM). Genotype–phenotype correlation studies show significant variability in the phenotype expression of HCM among affected individuals with identical causal mutations. Overall, causal mutations account for a fraction of the variability of phenotypes and genetic background, referred to as the modifier genes, play a significant role. The final phenotype is the result of interactions between the causal genes, genetic background (modifier genes), and probably the environmental factors. The individual modifier genes for HCM remain largely unknown, and a large-scale genome-wide approach and candidate gene analysis are needed. Current studies are limited to simple polymorphism association studies, which explore the association of functional single nucleotide polymorphisms in genes implicated in cardiac growth with the severity of the clinical phenotypes, primarily cardiac hypertrophy. Several potential modifier genes including genes encoding the components of the renin-angiotensin-aldosterone system have emerged. The most commonly implicated is an insertion/deletion polymorphism in the angiotensin-1 converting enzyme 1 gene, which is associated with the risk of sudden cardiac death and the severity of hypertrophy. Therapeutic interventions aimed at targeting the modifier genes have shown salutary effects in animal models of HCM. It has now recognized that modifier genes affect the expression of cardiac phenotype. Identification of the modifier genes will complement the results of studies of causative genes and could enhance genetic based diagnosis, risk stratification, and implementation of preventive and therapeutic measures in patients with HCM.

The phenotype of single gene disorders, particularly autosomal dominant disorders, is affected by genetic factors other than the causal mutation. Genetic background, often referred to as the modifier genes, is known to affect the phenotypic expression of monogenic disorders, such as hypertrophic cardiomyopathy (HCM). Modifier genes do not cause the disease but simply affect the severity of its phenotypic expression. This is particularly so with autosomal dominant disorders in which age-dependent onset and variable expressivity are characteristic. In the case of HCM, mutations in contractile sarcomeric proteins are necessary to cause HCM; however, the contribution of the causal mutations to the severity of phenotype can be relatively modest, with the modifier genes (genetic background) playing a significant role. It is now recognized that although the phenotype of any single gene disorder predominantly determined by the causal mutation, it is also markedly influenced by its interactions with other modifying genes and the environment. An overview of the causal genes and mutations and our current understanding of the pathogenesis of HCM will lay the background to illustrate and understand the role of the modifier genes in affecting the phenotypes in HCM.

Clinical phenotype of hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is an autosomal dominant disease with protean clinical manifestations that range from an asymptomatic course to that of severe heart failure and sudden cardiac death (SCD). HCM is diagnosed clinically by the presence of left ventricular hypertrophy in the absence of an increased external load (unexplained hypertrophy) and pathologically by the presence of myocyte hypertrophy, disarray, and interstitial fibrosis [1•]. Although hypertrophy and fibrosis are the common responses of the heart to all forms of injury, myocyte disarray is considered the pathologic hallmark of HCM [2•]. Cardiac hypertrophy and interstitial fibrosis are the major determinants of mortality and morbidity in HCM [3•,4•,5•]. In those with mild or no cardiac hypertrophy, myocyte disarray is a major predictor of SCD [6].

The clinical manifestations of HCM are variable. Most patients are asymptomatic or mildly symptomatic. The main symptoms are dyspnea, chest pain, palpitations, and infrequently syncope. Cardiac arrhythmias, in particular atrial fibrillation and nonsustained ventricular tachycardia, are relatively common and Wolff–Parkinson–White syndrome is present in approximately 5%. SCD is often the first manifestation of HCM in the young [7•]. Results of a physical examination may be completely normal or detect subtle abnormalities, particularly in patients without significant hypertrophy or left ventricular outflow tract obstruction. The typical arterial pulse has two components of percussion and tidal waves. The jugular vein may show a prominent *a* wave, reflective of poor right ventricular compliance. Apical impulse is strong and commonly bifid. A harsh, crescendo–decrescendo midsystolic murmur in the left sternal border is the most common and often the only finding. The murmur rarely radiates to carotid arteries, and its intensity changes with maneuvers that affect left ventricular volume or contractility. A loud S4 is commonly present.

Hypertrophic cardiomyopathy is the most common cause of SCD in competitive athletes [7•]. In the adult population, HCM is a relatively benign disease with an estimated annual mortality rate of less than 0.7% [8]. Cardiac hypertrophy is a major determinant of morbidity and mortality in HCM [4•]. It is not only a predictor of SCD, but also in conjunction with interstitial fibrosis leads to an increased left ventricular end diastolic pressure (diastolic dysfunction) and symptoms of heart failure.

Prevalence of hypertrophic cardiomyopathy

The true prevalence of HCM is unknown. It is estimated approximately 1 of 500 individuals between the ages of 25 and 35 years have HCM, as detected by the presence of unexplained cardiac hypertrophy on echocardiography [9•]. The prevalence of HCM is likely to be much higher in older subjects, because the penetrance is age dependent and affected individuals gradually exhibit the phenotype as they get older [10,11•].

Diversity of cardiac phenotypes in hypertrophic cardiomyopathy

Although cardiac hypertrophy is the primary clinical phenotype that leads to the diagnosis of HCM, morphologic and pathologic features of HCM encompass a diverse array of phenotypes. Left ventricular hypertrophy is concentric and often asymmetric. Hypertrophy is often more severe in the interventricular septum, which often in combination with other factors, leads to outflow tract obstruction and intracavity gradient. Occasionally, hypertrophy is restricted to the apex and the ensuing phenotype is referred to as apical HCM. The latter phenotype has been reported more often in the Japanese population. Extent of cardiac hypertrophy is variable not only among members of different families but also among members of each family [12•], an observation that suggests involvement of factors other than the causal mutations. Acceleration of evolution of cardiac phenotype during adolescence and puberty also implicates

involvement of growth factors in modulating expression of hypertrophy in HCM [11•,13]. Similarly to hypertrophy, myocyte disarray is more prominent in the interventricular septum. Myocyte disarray, which is often scattered throughout the myocardium, comprises more than 20% to 30% of the myocardium in HCM [2]. Other morphologic and histologic features of HCM include interstitial fibrosis, thickening of the media of intramural coronary arteries, abnormal positioning of the mitral valve annulus, and elongated mitral leaflets, among others.

Molecular genetic basis of HCM

Hypertrophic cardiomyopathy is a genetic disease with an autosomal dominant mode of inheritance. Family history of HCM is present in approximately two thirds of all index cases; thus, HCM is familial. In the remainder, it is caused by *de novo* mutations and thus it presents as a sporadic case. Accordingly, sporadic cases are also genetic disorders, and the affected individuals could transmit the mutation and thus the disease to their offspring. Genetic studies suggest that mutations arise independently and there is no common founder [14,15]. HCM, defined as hypertrophy in the absence of an increased external load, could also occur because of mutations in the mitochondrial genome [16], which will exhibit a matrilinear transmission as well as in conjunction with triplet repeat syndromes [17].

Mutations in contractile sarcomeric proteins

The R403Q missense mutation in the β -myosin heavy chain gene was the first causal mutation identified for HCM [18•]. Subsequently mutations in other components of thin and thick filaments of sarcomere were discovered, which collectively led to the notion that HCM is a disease of contractile sarcomeric proteins [19•]. To date, more than 100 different mutations in 11 genes encoding contractile sarcomeric proteins have been identified in patients with HCM (Table 1).

Genes encoding β -myosin heavy chain (*MYH7*), myosin binding protein C (*MYBPC3*), and cardiac troponin T (*TNNT2*) are the three most common causal genes for HCM. Collectively, mutations in them account for approximately three fourths of all HCM cases. The *MYH7* is the most common gene, accounting for approximately 35% to 50% of all HCM cases [1•] and codons 403 and 719 in myosin binding protein-C are considered hot spots for mutations [20, 21]. Most of the mutations are located in the globular head of the myosin molecule and are missense mutations [22,23]. Deletion mutations and an insertion/deletion mutation changing amino acids 395–404 in the rod and tail regions also have been described [23,24]. The frequency of each particular *MYH7* mutation is relatively low.

MYBPC3 gene on chromosome 11 [25•] accounts for approximately 20% to 25% of all HCM cases and probably is the second most common causal gene for human HCM [11•,12•,26•]. More than 40 different mutations in the *MYBPC3* gene have been identified and the majority are deletion/insertion or splice junction mutations [26•], which result in frame-shift or truncation of the MyBP-C proteins. Founder effect is uncommon, and the frequency of each mutation is low [11•,25•,26•,27,28]. Another relatively common causal gene for human HCM is the *TNNT2* gene on chromosome 1q3, which encodes cardiac troponin T. Mutations in cardiac troponin T account for approximately 20% of all HCM cases, and the majority are missense mutations [19•,29].

Mutations in other components of thin and thick filaments of sarcomeres are uncommon causes of HCM. The list include genes encoding troponin I [30,31], α -tropomyosin [19,32,33], troponin C [34], cardiac α -actin (*ACTC*), [35•,36], titin (*TTN*) [37], MLC1 (*MYL3*) [38], and MLC2 (*MYL2*) [38,39].

Mutations in nonsarcomeric proteins

Recently, mutations in genes encoding for AMP-activated $\gamma 2$ noncatalytic subunit of protein kinase A (AMPK), a regulator of cell bioenergetics, have been identified in families with HCM and Wolff–Parkinson–White syndrome (Table 2)[40•,41•]. The described phenotype varies from that of preexcitation and conduction defects and minimal hypertrophy to that of severe and early-onset hypertrophy with a minority of patients showing preexcitation.

Mutations in mitochondrial DNA

Mutations in mitochondrial genome have been associated with HCM [42]. Commonly, mutations in mitochondrial DNA often cause a complex phenotype that involves multiple organs including the heart [42]. Because each mitochondrion has multiple copies of its own DNA and each cell contains thousands of mitochondrial DNA, mutations result in a significant degree of heteroplasmy (combination of wild-type and mutant mitochondrial DNA), which confounds establishing the causality. Overall, it is estimated that more than 80% to 90% of mitochondrial DNA needs to mutate before it causes a significant clinical phenotype [43•]. Kearns-Sayre syndrome, characterized by a triad of progressive external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction defects, is an example of mitochondrial disease [16]. The classic cardiac abnormality in Kearns-Sayre syndrome is conduction defects. However, dilated and hypertrophic cardiomyopathies are also often observed but at a lower frequency.

Triplet repeat mutations

Hypertrophic cardiomyopathy is also often observed in patients with the triplet repeats syndromes, such as myotonic muscular dystrophy and Friedreich ataxia [17]. Triplet repeats syndromes are a group of neuromuscular disorders caused by an expansion of trinucleotide repeat sequences in their respective genes (Table 2). Myotonic muscular dystrophy and Friedreich ataxia are two examples of triplet repeat syndromes that also involve the heart. Myotonic dystrophy is the most common form of muscular dystrophy in adults and commonly manifests as progressive degeneration of muscles and myotonia, cardiomyopathy, male pattern baldness, infertility, premature cataracts, and mental and endocrine abnormalities [17]. Cardiac involvement is common and includes conduction defects, dilated cardiomyopathy, and less often HCM [44]. It is an autosomal dominant disorder caused by an expansion of GCT trinucleotide repeats, from less than 40 in normal individuals to more than several hundreds and thousands, in the 3' untranslated region of dystrophin myotonia protein kinase (*DMPK*) gene [17]. Similarly, Friedreich ataxia is an autosomal recessive neurodegenerative disease caused by the expansion of GAA trinucleotide repeats located within intron 1 of the *FRDA* gene [45]. The gene encodes frataxin, which is a soluble mitochondrial protein with 210 amino acids [45]. Friedreich ataxia involves both central and peripheral nervous system, and cardiac involvement includes dilated and hypertrophic cardiomyopathy. In triplet repeats syndromes, the severity of clinical manifestations including cardiac phenotype correlates with the size of the repeats [46].

Collectively, these data suggest that HCM, defined as hypertrophy in the absence of an increased external load, occurs primarily as a result of mutations in genes encoding the contractile sarcomeric proteins. HCM, often in conjunction with other cardiac and noncardiac phenotypes, also occurs because of mutations in nonsarcomeric proteins, such as mitochondrial DNA and triplet repeats. Thus, HCM, a genetic model of cardiac hypertrophy, is caused by a diverse array of mutations in a variety of genes.

Impacts of causal genes and mutations on phenotypes

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 [22,26•,47–51]. 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 [11•,52•]. In contrast, mutations in the MyBP-C are associated with a relatively mild hypertrophy and late onset of clinical manifestations [11•,26•,52•]. Mutations in *MYBPC3* gene are often associated with a low penetrance, mild hypertrophy, and a low incidence of SCD [11•]. The phenotype often develops late, which may coincide with the concomitant presence of hypertension. Despite the overall benign nature of mutations in the MyBP-C, significant variability in the phenotypic expression of HCM exists and the so-called malignant mutations also have been reported in the *MYBPC3* genes [26•]. Mutations in cardiac troponin T are usually associated with a mild degree of hypertrophy but a high incidence of SCD and more extensive disarray [6,50•]. Mutations in α -tropomyosin are generally associated with a benign phenotype and mild left ventricular hypertrophy. Despite mild degree of hypertrophy, a high incidence of SCD also has been described [33]. Mutations in essential and regulatory myosin light chains have been associated with midcavity obstruction in HCM and skeletal myopathy in some [38] but not in others [39]. Mutations in titin [37] and α -actin [35•,36] have been observed in a small number of families. With regard to HCM caused by mutations in *PRKAG2*, the phenotype is variable. In some families, the predominant phenotype is preexcitation and conduction abnormalities [40], and cardiac hypertrophy is present in the minority of the patients [40•]. In others, early cardiac hypertrophy predominates and preexcitation is present in a fraction of the cases [41•].

Mutations, regardless of the causal gene or mutation, exhibit an age-dependent penetrance. Therefore, a normal physical examination and clinical testing at an early age do not effectively exclude the possibility of developing HCM later in life [10]. This is particularly the case for HCM caused by mutations in MyBP-C, because the phenotype often develops in the fifth or sixth decades of life [10]. In general, mutations associated with milder hypertrophy, late onset of HCM, and a low penetrance are associated with a relatively benign prognosis [53]. In contrast, those associated with more extensive hypertrophy, high penetrance, and an early age of onset of HCM carry a higher risk of SCD.

The results of genotype–phenotype correlation studies are subject to a large number of confounding factors, such as the small size of the families, small number of families with identical mutations because of low frequency of each mutation, variability in the phenotypic expression in affected individuals within the same family or among families with identical mutations, influence of modifier genes, influence of nongenetic factors, and rarely, homozygosity for causal mutations and compound mutations [54,55]. Collective data indicate that mutations exhibit highly variable clinical, electrocardiographic, and echocardiographic manifestations, and no particular phenotype is mutation specific [12•].

Pathogenesis of hypertrophic cardiomyopathy

In keeping with the diversity of the causal genes and mutations, the initial defects induced by the mutant sarcomeric proteins are also diverse. The initial defect may be mechanical (actomyosin interaction and cardiac myocyte contractile performance), biochemical (Ca^{+2} sensitivity) bioenergetic (ATPase activity), and/or structural (sarcomere assembly, subcellular localization, and stoichiometry; reviewed in [56•]). Despite the diversity of the initial defects, they converge into a common phenotype of compensatory hypertrophy, fibrosis, and disarray (for review see [57]). The common link between the initial defect and the final phenotype is impaired cardiac myocyte mechanical function [58•], which increases myocyte stress and leads to activation of stress-responsive intracellular signaling kinases and trophic factors in the heart.

Collectively, stress-responsive signaling kinases and trophic factors activate the transcription machinery leading to cardiac hypertrophy, interstitial fibrosis, and other histologic and clinical phenotypes of HCM [58•]. Accordingly, myocyte hypertrophy and disarray, interstitial fibrosis, and thickening of the media of intramural coronary arteries are considered secondary phenotypes, and thus their development could be affected by factors other than the causal genes, (*ie*, the environmental factors and the modifier genes).

Modifier genes

Modifier genes are genes other than the causal genes that affect the phenotypic expression of genetic disorders. Modifier genes are the genetic background of the affected individuals, which differs because of the presence of DNA polymorphism. Modifier genes are neither necessary nor sufficient to cause HCM, but rather they affect the severity of HCM phenotypes, such as the extent of hypertrophy and the risk of SCD.

The influence of genetic background on cardiac hypertrophic response has been shown previously through epidemiologic and family studies in humans [59,60] and experimental data in animals [61,62]. Clinical observations showing a significant degree of variability in the phenotypic expression of hypertrophy, sudden death, and cardiac failure in patients with HCM, a genetic model of cardiac hypertrophic response, underscore the influence of modifier genes on cardiac phenotypes. This is particularly evident when individuals with identical causal mutations or the affected members of families who share identical mutations exhibit a significant degree of variability in the phenotypic expression of the disease. An example of such degree of variability is illustrated in Figure 1, which shows large variability in cardiac mass index among sibs and other affected members of a family with a mutation in the MyBP-C. The variability indicates that factors other than the causal mutations modulate phenotypic expression of hypertrophy in HCM. This notion is also in accord with the experimental and clinical data suggesting that cardiac hypertrophy, the clinical hallmark of HCM, and, in addition, other histologic and morphologic phenotypes are compensatory and thus likely to be modulated by a large number of factors [58•]. Similarly, variability in the age-dependent penetrance and acceleration of evolution of cardiac phenotype during puberty and adolescence suggest involvement of factors other than the causal genes such as the growth factors in modulating cardiac hypertrophic response in HCM. Thus, although HCM is a classic example of monogenic disorders, expression of multiple genes is likely to affect its phenotypic expression. The final phenotype is the product of the causal mutations, modifier genes, and environmental factors. Thus, given the significance of the modifier genes in modulating cardiac phenotypes in HCM, their identification and characterization of their role will complement the primary (causal) mutation in predicting prognosis and could be essential for designing specific and more comprehensive therapy.

Gene variants as the modifiers

Completion of the Human Genome Project has ushered in new opportunities to identify single nucleotide polymorphisms (SNPs) and develop SNP and haplotype maps of the genome to map the genetic determinants of quantitative traits, including those of monogenic disorders [63]. Similarly, identification of genetic factors other than the causal genes that affect expression of the phenotypes in HCM will be facilitated through construction of SNP and haplotype map of the human genome. The National Center for Biotechnology Information, in collaboration with the National Human Genome Research Institute, has established the dbSNP database, which serves as a central repository for both single base nucleotide substitutions and short deletion and insertion polymorphisms. As of December 13, 2001, 4,116,037 SNPs in the human genome have been submitted to this site (<http://www.ncbi.nlm.nih.gov/SNP/overview.html>). Another database called The SNP Consortium Ltd. was established in 1999 through collaboration of 11 major pharmaceutical

and technology companies, one large scientific trust, and 4 major centers for genetics. The goal of this consortium is to develop up to 300,000 SNPs distributed evenly throughout the human genome. Thus far, 1,255,326 SNPs, available in a database maintained by the Cold Spring Harbor Laboratory, have been anchored to the human genome (<http://snp.cshl.org/index.html>).

It is estimated that the human genome contains approximately 30,000 to 50,000 genes and more than 1.6 million nonredundant SNPs [63,64•]. Each gene has multiple SNPs that cooperatively regulate its expression and affect function of the encoded protein. For example, the human gene encoding the angiotensin-1 converting enzyme 1 (ACE-1) has at least 13 SNPs that collectively affect ACE-1 levels and its function [65]. In addition, given the diversity of the regulatory factors, the impact of each SNP on gene expression is expected to be modest. Furthermore, SNPs in a given gene may exert additive, synergistic, or subtractive effects on expression or function of the protein or may interact with SNPs in other genes. Moreover, epigenetic and environmental factors could affect the impact of SNPs on gene expression and protein function. At the genetic level, a significant number of SNPs in each gene are in linkage disequilibrium (cosegregate together) and thus genotyping for a fraction of all SNPs of a gene may be sufficient to construct the main haplotypes of a gene [66,67]. Nevertheless, comprehensive analysis of SNPs in each candidate modifier gene is necessary to delineate its modifying effects.

The identity of the modifier genes for HCM and the magnitude of their effects have not been systematically explored. Because of the complexity of regulation of gene expression and that of the molecular biology of cardiac hypertrophy, a large number of genes and their functional variants are expected to modify expression of cardiac phenotypes in HCM, each exerting a modest effect. Complex genotype–genotype and genotype–environment interactions could further influence the phenotypic expression of HCM and complicate the genetic studies aimed at identifying the modifier genes for HCM. Overall, the genetic approach to map the modifier genes for single-gene disorders could be categorized as genome-wide approach and candidate gene approach. Each approach has its own limitations and advantages and will be discussed briefly.

Genome-wide approaches to identify modifier genes for hypertrophic cardiomyopathy

A genome-wide approach is used to map the modifier loci in the absence of *a priori* knowledge of their chromosomal location. Genome-wide approaches are based on analyzing segregation of polymorphic DNA markers positioned throughout the genome with the severity of a phenotype. The conventional genetic linkage analysis, which has markedly accelerated our search for the causal genes for single gene disorders, often has inadequate power to map the modifier genes. Several mathematical techniques have been developed and assessed for their sensitivity and accuracy in detecting multiple modifying loci. The principle behind the techniques of genome-wide search is based on quantitative trait loci analysis in which segregation of the DNA markers with the severity of the phenotype is analyzed. The genome-wide approach could be applied to genetically independent cases through association studies or in a single family or families with the disease, taking into considerations the genetic interdependence of the subjects. Genome-wide techniques could simultaneously localize and parameterize several genetic loci using an oligogenic model. Family data could be analyzed and the total number of loci, including both causative and modifier loci, that contribute to variation in the trait of interest, such as hypertrophy, could be estimated. These methods also permit incorporating factors that already are known to affect the phenotype, which enhances the ability to estimate the location and effect of additional modifiers. Unlike traditional linkage methods, these methods attempt to model the effects of all loci that contribute to a trait; so

multiple causative and modifier loci can be included in a single analysis without significant confounding effects arising from genetic heterogeneity.

Candidate gene approach

Unlike genome-wide studies, the candidate gene approach requires *a priori* knowledge of the potential involvement of the specific genes in the pathogenesis of the trait of interest. Candidate genes are often selected based on the evidence driven from molecular biology studies implicating a specific molecule in the pathogenesis of the trait. Commonly, the association of biologically functional SNPs and haplotypes in the candidate gene with the phenotype is analyzed in a prospective study, which is more robust than case-control studies. The aim of an association study is to show that a functional variant of the candidate gene is associated with the presence or severity of the phenotype, and affects the clinical outcome or response to treatment (pharmacogenetics). A positive association does not establish the causality, and often the associated marker is in linkage disequilibrium with the risk-allele. Linkage disequilibrium simply illustrates a nonrandom segregation of two DNA markers and frequently occurs when two markers (the associated allele and the true mutation) are in close genetic proximity on a chromosome. Thus, they cosegregate more often than expected by chance alone.

The strength of the SNP association studies is their ability to detect modest effects of the modifier genes, which is in contrast to the conventional linkage techniques that have limited power to map genes with small or moderate effects. Because SNPs do not exist in isolation and multiple SNPs interact and regulate gene expression, it is often necessary to construct chromosomal haplotype for association studies. The availability of regional and genome-wide SNP and haplotype maps of human genome will afford the opportunity to perform comprehensive association studies of the candidate modifier genes and chromosomal regions [66,67]. Unfortunately, SNP association studies, whether used for genome-wide or candidate gene analysis, are subject to multiple confounding factors and have a high rate of spurious results. This is particularly problematic in retrospective case-control allelic association studies performed in a small sample size. A large number of confounding factors affect the results including population characteristics, design of the study, sample size, multiple hypothesis testing, biologic plausibility, functional significance of the SNPs, strength of the association, presence of genetic and biologic gradients, and others [68•]. Because of inherent weaknesses of association studies with SNPs, the results are considered provisional and require confirmation in duplication studies and through experimentation [69•].

Candidate modifier genes

In view of the increasing evidence showing the significance of the modifier genes in modulating the phenotype of single gene disorders, recently the National Institute of Health initiated and sponsored several research programs to identify the individual modifier genes for single-gene disorders, including cardiomyopathies. Thus far, no systematic study has been performed to map the modifier genes for human HCM, and the existing data are limited to the results of several SNP-association studies in several candidate genes.

Single nucleotide polymorphism association studies have implicated several genes as the candidate modifiers for HCM (Table 3)[70–72]. The results suggest that functional variants of ACE-1 gene are associated with an increased risk of SCD [73•] and the severity of left ventricular hypertrophy [74]. Variants of endothelin-1 and tumor necrosis factor- α also have been associated with the severity of the cardiac hypertrophy in HCM [75,76]. SNPs in several other genes also have been associated with the clinical phenotypes of HCM. Overall, the results have been inconsistent, perhaps because of the small sample size of the study, population characteristics, and several other potential confounders that are frequently encountered in SNP-association studies, as discussed earlier. Given the uncertainties associated with the results of

the SNP-association studies, we will avoid discussing each potential modifier gene and limit the discussion to the ACE-1 gene, which is the most commonly studied candidate modifier gene and has the best supportive evidence as compared with others.

Genes coding for ACE-1 and the other components of the renin–angiotensin–aldosterone system are biologically plausible candidate modifiers for human HCM because of the well-established role of renin–angiotensin–aldosterone in the cardiovascular system, including the expression of cardiac hypertrophy. ACE-1 is a transmembrane-ectopeptidase that catalyzes the conversion of angiotensin-I to angiotensin II (AT) and inactivates bradykinin. Angiotensin II and bradykinin exert strong autocrine and paracrine effects in opposing directions. Although angiotensin II promotes growth and hyperplasia, bradykinin is a cardioprotective agent [77]. ACE-1 is upregulated in pressure overload induced–cardiac hypertrophy and in heart failure [78]. Inhibition of ACE-1 induces regression of cardiac hypertrophy independent of load and prevents dilatation and remodeling of the ventricle after myocardial infarction [79]. Recently, an insertion (I)–deletion (D) polymorphism in the ACE-1 gene was identified because of the presence or absence of 287-bp Alu repeats in intron 16, which results in three genotypes of DD, ID, and II [80•]. The I/D polymorphism is considered a functional polymorphism because it exerts a co-dominant effect on the plasma, tissue, and cellular levels of ACE-1 [80•]. Patients with the DD genotype have the highest, those with the ID the intermediary, and those with the II genotype have the lowest plasma and tissue levels of ACE-1 [80•].

Since description of the first study suggesting a potential modifier role for the ACE-1 gene in HCM approximately 10 years ago, a large number of studies have explored the association of the I/D polymorphism with expression of the clinical phenotypes in HCM [73•,74,81–85]. The initial report showed an association between the I/D genotypes and the risk of SCD in patients with HCM [73•]. The DD genotype was more common in HCM families with a high incidence of SCD as compared with those with a low incidence of SCD [73•]. Subsequent studies provided further evidence of the modifying effects of the ACE-1 gene by showing an association between the I/D genotypes and the severity of cardiac hypertrophy HCM [74,81]. Indices of cardiac hypertrophy, namely, the mean interventricular septal thickness, the mean left ventricular mass index (indexed to body surface area), and a semiquantitative index of left ventricular hypertrophy, referred to as the Wigle score, were greater in HCM patients with the DD genotype as compared with others [74,81]. The observed association followed a gradient consistent with the gene-dose effect (DD>ID>II) and was in accord with the known dose-dependent association of the I/D polymorphism with the plasma and tissue levels of ACE-1 [74]. The frequency of the DD genotype correlated with the severity of cardiac hypertrophy, as shown in Figure 2. In a general population of HCM, the overall impact of the ACE-1 genotypes on expression of cardiac hypertrophy was relatively small, and the I/D genotypes accounted for approximately 5% the variability of indices of hypertrophy. The impact of the I/D genotypes on expression of cardiac hypertrophy was greater in the affected members of a single family accounting for approximately 10 to 15% of the variability of the indices of hypertrophy [74]. The results of another study suggest that the association of the ACE-1 I/D genotypes with the expression of cardiac hypertrophy is dependent on the causal mutation, and a significant association is present in those with the R403Q mutation in the β -myosin heavy chain but not in others [81]. Several other studies also have shown an association between the ACE-1 I/D genotypes and indices of cardiac hypertrophy in HCM, whereas others have not [84,85]. In addition, the frequency of the I/D genotypes among cases and controls has been compared and the results have been conflicting (Table 3).

Potential significance of the modifier genes as therapeutic targets

Recent studies suggest that pharmacologic blockade of modifier genes could confer beneficial effects in HCM. Pharmacologic interventions in transgenic animal models of HCM aimed at

the potential modifier genes provide further support to the role of modifier genes in the pathogenesis of morphologic and histologic phenotypes in HCM. In a recent randomized study we showed that blockade of angiotensin II receptor 1 in the cardiac troponin T-Q92 transgenic mouse model reduced interstitial collagen volume by 49% and expression of collagen $\alpha 1$ (I) mRNA and transforming growth factor- $\beta 1$, a known mediator of profibrotic effects of angiotensin II, by approximately 50% [86•]. This finding, in conjunction with the result of genetic association studies, implicates components of the renin–angiotensin–aldosterone system in modulating cardiac phenotype in HCM. The significance of this finding is severalfold. It illustrates that interventions aimed at the modifier genes could affect the phenotype. Because interstitial fibrosis is considered a major risk factor for SCD and ventricular arrhythmias in human patients with HCM [3•,87], this finding suggest that blockade of modifier genes could affect the risk of SCD and mortality in HCM. It is noted that despite the well-established role of blockade of renin–angiotensin–aldosterone system in reversal of cardiac fibrosis in a variety of cardiovascular diseases, they are not currently used in treatment of human patients with HCM. The concern arises from the possible worsening of outflow gradient because of afterload reduction with these agents.

Pharmacologic interventions that block the modifier genes involved in the pathogenesis of cardiac hypertrophy could potentially attenuate cardiac hypertrophy and fibrosis in HCM. In a randomized study, we showed that simvastatin, a pleiotropic 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitor, reduced mean left ventricular mass by 37%, septal and posterior wall thickness by approximately 20%, and collagen volume fraction by approximately 50% in the β -myosin heavy chain-Q403 transgenic rabbit model of human HCM [88•]. Indices of left ventricular filling pressure were improved significantly. The salutary effects of simvastatin were associated with a significant reduction in expression of active ERK1/2. Thus, therapies aimed at modifier genes could induces regression of cardiac hypertrophy and fibrosis and improve cardiac function, major predictors of mortality and SCD, in human patients with HCM [3•,4•].

Acknowledgments

This work is supported in part by National Heart, Lung, and Blood Institute, Specialized Centers of Research grants P50-HL42267-01 and 1R01HL/DK68884-01.

Abbreviations

ACE-1, angiotensin-1 converting enzyme 1; HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; SNPs, single nucleotide polymorphisms.

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Figure 1. Variability of expression of hypertrophy in family members with hypertrophic cardiomyopathy caused by a mutation in the myosin binding protein C

A truncated pedigree is shown. Affected individuals are shown in black circles (female) and squares (males). As shown, affected members within the same generation show significant variability in the magnitude of left ventricular mass index.

Figure 2. Association of the DD genotype of angiotensin-1 converting enzyme 1 gene with left ventricular mass index in genetically independent (index) cases of hypertrophic cardiomyopathy. As shown, the frequency of the DD genotype increases as the left ventricular mass index increases in the population.

Table 1

Causal genes for hypertrophic cardiomyopathy (HCM): genes coding for sarcomeric proteins

Gene	Symbol	Locus	Frequency	Mutations
β-Myosin heavy chain	<i>MYH7</i>	14q12	~35%	>70, Predominantly missense mutations
Myosin binding protein-C	<i>MYBPC3</i>	11p11.2	~20%	>40, Predominantly splice junction and insertion/deletion mutations
Cardiac troponin T	<i>TNNT2</i>	1q32	~20%	>15, Mostly missense
α-Tropomyosin	<i>TPM1</i>	15q22.1	~5%	>5 Missense mutations
Cardiac troponin I	<i>TNNI3</i>	19p13.2	~5%	3 Missense and 1 deletion mutations
Essential myosin light chain	<i>MYL3</i>	3p21.3	<5%	2 Missense mutations
Regulatory myosin light chain	<i>MYL2</i>	12q23–24.3	<5%	7 Missense and 1 truncation mutations
Cardiac α-actin	<i>ACTC</i>	15q11	<5%	2 Missense mutations
Titin	<i>TTN</i>	2q24.1	<5%	1 Missense mutation
α-Myosin heavy chain	<i>MYH6</i>	14q1	Rare	1 Missense and 1 rearrangement mutations
Cardiac troponin C	<i>TNNC1</i>	3p21.3–3p14.3	Rare	1 Missense mutations in a patient with HCM

Table 2

Causal genes for hypertrophic cardiomyopathy: genes coding for nonsarcomeric proteins

Gene	Symbol	Locus	Frequency	Mutations
AMP-activated protein kinase, γ 2 regulatory subunit	<i>PRKAG2</i>	7q35-q36	<5%	3 Point and 1 insertion mutations
Mitochondrial DNA	<i>MTT1</i>	Mitochondrial	Rare	tRNA Isoleucine and tRNA glycine
Frataxin (Friedreich ataxia)	<i>FRDA</i>	9q13		>200 GAA in intron 1
Myotonin protein kinase (myotonic dystrophy)	<i>DMPK</i>	19q13	Uncommon	>50 CTG in 3'-UTR

Table 3

Genes that are candidate modifiers for hypertrophic cardiomyopathy (HCM)

Gene	Symbol	Locus	Polymorphism	Results
Angiotensin-1 converting enzyme-1	<i>ACE</i>	17q23	I/D	DD is associated with higher risk of SCD [73] DD is associated with severity of hypertrophy [74,81] DD is more common in HCM patients [82,83] Frequency of DD genotype unchanged [84]
Angiotensinogen	<i>AGT</i>	1q42	–6G/A T174M M235T	No association with indices of hypertrophy [84,85] No association with indices of hypertrophy [75,84] 235T allele more common in HCM [70]
Angiotensin II receptor 1	<i>AGTR1</i>	3q21–q25	1166A/C	Frequency of T174M and M235T unchanged [84] No association with indices of hypertrophy [75] C allele is associated with severity of hypertrophy [85]
Chymase	<i>CMA1</i>	14q11.1	1625A/G	No changes in frequency in HCM [82]
Bradykinin B2 receptor	<i>BDKRB2</i>	14q32.1–q32.2	–412C/G T21M	T21M was found in HCM cases but not in controls [71]
Aldosterone synthase	<i>CYP11B2</i>	8q21–q22	–344T/C	No association with indices of hypertrophy [76]
Endothelin-1	<i>EDN1</i>	6p24.1	8002G/A	A allele is associated with severity of hypertrophy [75]
Tumor necrosis factor α	<i>TNF</i>	6p21.3	–308G/A	A allele is associated with severity of hypertrophy [76]
Insulin-like growth factor 2	<i>IGF2</i>	11p15.5	820G/A	No association with indices of hypertrophy [76]
Transforming growth factor β 1	<i>TGFB1</i>	19p13.2	–509C/T	No association with indices of hypertrophy [76]
Interleukin 6	<i>IL6</i>	7p21	–174G/C	No association with indices of hypertrophy [76]
Platelet activating factor acetylhydrolase	<i>PLA2G7</i>	6p21.2–p12	994G/T (V279T)	T allele is more common in HCM and is associated with increased left ventricular dimension and decreased function [72]