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Genetic determinants of cardiac hypertrophy

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Abstract

Purpose of review—Cardiac hypertrophy is a common phenotypic response of the heart to stimulants. It is associated with increased morbidity and mortality in various cardiovascular disorders. Genetic factors are important determinants of phenotypic expression of cardiac hypertrophy, whether in single-gene disorders or in complex traits. We focus on the molecular genetics of cardiac hypertrophy in various conditions with an emphasis on hypertrophic cardiomyopathy, a genetic paradigm of cardiac hypertrophic response.

Recent findings—The molecular genetic basis of cardiac hypertrophy in single-gene disorders has been partially elucidated. Likewise, the impact of genetics on the expression of cardiac hypertrophy in the general population has been demonstrated. Identification of mutations in the Z disk proteins has expanded the spectrum of causal mutations beyond the thin and thick filaments of the sarcomeres. In addition, modifier loci have been mapped and shown to impart considerable effects on the expression of cardiac hypertrophy in hypertrophic cardiomyopathy. Elucidation of the molecular genetics of sarcomeric hypertrophic cardiomyopathy and many of the phenocopies has highlighted the limitations of clinical diagnosis as a determinant of management and prognostic advice. The findings have raised the importance of diagnosis and treatment algorithms, which are based on both genotype and phenotype information.

Summary—Cardiac hypertrophy, regardless of the cause, is the phenotypic consequence of complex interactions between genetic and nongenetic factors.

Keywords

genetic; hypertrophy; modifier genes; mutation; polymorphism; sudden cardiac death

Introduction

Cardiac hypertrophy is defined as an increase in cardiac mass. It usually denotes an increase in the left ventricular mass or left ventricular hypertrophy (LVH). The primary cellular basis of cardiac hypertrophy is an increase in the size of the cardiac myocytes but not in the number, as adult myocytes are terminally differentiated cells [1]. The myocardium, however, contains a number of resident progenitor cells, which afford the heart considerable replicative and reparative capacity [2-5]. The role of myocyte progenitor cells in cardiac hypertrophy is unclear.

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At a cellular level, heart is a heterogeneous organ. There are approximately 20 million myocytes per gram of the myocardium [6]. Cardiac myocytes, because of their larger size, as compared with other cells, account for approximately two-thirds of the cardiac mass. Thus, cardiac hypertrophy is primarily the result of myocyte hypertrophy. Myocardium also comprises fibroblasts, circulating blood cells, endothelial cells, smooth muscle cells and others that collectively outnumber cardiac myocytes by a ratio of 2 : 1. Often, the stimulus that leads to myocyte hypertrophy also leads to proliferation of cardiac fibroblasts and hence interstitial fibrosis. Accordingly, pathological cardiac hypertrophy is usually accompanied by interstitial fibrosis.

Morphologically, LVH follows two general patterns of concentric and eccentric hypertrophy. Concentric hypertrophy is characterized by an increase in wall thickness, whereas the left ventricular cavity is small or normal in size. A prototypic example of concentric hypertrophy is hypertrophic cardiomyopathy (HCM). In contrast, in eccentric hypertrophy, the predominant increase is in the left ventricular chamber size with mild or no increase in wall thickness. Dilated cardiomyopathy (DCM) typifies the eccentric hypertrophy. Myocyte hypertrophy also follows the two patterns of concentric and eccentric hypertrophy. In concentric myocyte hypertrophy, the predominant increase is in the cell width because of the addition of sarcomeres in parallel. In contrast, in eccentric myocyte hypertrophy, myocyte length is increased because of the addition of sarcomeres in series. An increase in cardiac mass could also occur because of the deposition of glycogen or polysaccharides in myocytes, as in storage diseases. Perhaps it is better to classify these conditions as pseudohypertrophy or phenocopies, as they arise from excess storage and not addition of sarcomeres.

The clinical significance of pathological cardiac hypertrophy is noteworthy. Cardiac hypertrophy, regardless of the cause or the ethnic background, is an important determinant of mortality, morbidity and the risk of sudden cardiac death (SCD) in all forms of cardiovascular diseases [7-10]. Cardiac hypertrophy is also an important determinant of diastolic heart failure, which is a major cause of mortality and morbidity, especially in the elderly [11]. Thus, elucidation of molecular genetics and pathogenesis of cardiac hypertrophy could have considerable impact on prevention and treatment of various cardiovascular diseases.

Molecular genetics

Cardiac hypertrophy is a complex phenotype. Hence, its expression is determined by the complex interactions of various genetic and nongenetic factors. The contribution of each component to the phenotype is context-dependent. In the so-called ‘pure’ forms of cardiac hypertrophy, the contribution of genetic factors is expected to outweigh that of the nongenetic factors. In contrast, in acquired forms such as valvular heart disease, the primary determinant is expected to be the load, whereas the genetic factors contribute to the severity of the hypertrophic response.

The molecular genetic basis of cardiac hypertrophy in single-gene disorders, such as HCM, has been mostly elucidated. Likewise, the influence of genetic factors in determining cardiac mass and the hypertrophic response in the general population has been documented. The estimates of heritability of the left ventricular mass in the general population vary from 20 to 70% [12-14,15]. The primary focus of this review is on the molecular genetic basis of human HCM, as a prototypic form of cardiac hypertrophy with a Mendelian pattern of inheritance. In addition, the genetic basis of other conditions wherein cardiac hypertrophy is a prominent feature is discussed briefly.

Hypertrophic cardiomyopathy as a genetic paradigm of cardiac hypertrophic response

HCM is a primary disease of the myocardium characterized by concentric and often asymmetric LVH with a predominant involvement of the interventricular septum. The left ventricular cavity is small, and systolic function is usually preserved. The pathological hallmark of HCM is myocyte disarray [16,17]. Cardiac hypertrophy, interstitial fibrosis and myocyte disarray are associated with an increased risk of SCD in HCM [11,18-20].

The estimated prevalence of HCM is approximately 1 : 500 in young individuals [21]. The prevalence is likely to be higher in the elderly as the penetrance of the causal mutations is age-dependent [22]. The clinical manifestations of HCM encompass heart failure, cardiac arrhythmias and SCD. SCD is the most dreaded and tragic phenotype as it is often the first manifestation of the disease and often occurs in asymptomatic and apparently healthy young individuals [23,24]. HCM is the most common recognizable cause of SCD in young competitive athletes [23]. Despite the risk of SCD, overall, HCM is a relatively benign disease with an annual mortality of less than 1% in the adult population [25,26].

Familial and sporadic HCM share a common genetic cause. The pioneering work of Drs Christine Seidman and Jonathan Seidman led to the discovery of the first causal mutation (R403Q) in *MYH7*, which encodes the β-myosin heavy chain (MyHC) [27]. The seminal discovery was soon followed by the discovery of mutations in *TNNT2* and *TPM1*, encoding cardiac troponin T and α-tropomyosin, respectively [28]. The discoveries implicated HCM as a disease of the sarcomeric proteins. Subsequently, over a dozen causal genes and several hundred mutations were identified (Table 1). The causal genes (excluding the phenocopy conditions) encode thin and thick filament and the Z disk proteins of the sarcomeres.

The two most common causal genes for HCM are *MYH7* and *MYBPC3*, the latter encoding myosin-binding protein C [29-31]. Collectively, these two genes account for 50–60% of all cases of HCM [29-31]. Mutations in *TNNT2*, encoding cardiac troponin T, *TNNI3*, encoding cardiac troponin I, and *TPM1*, encoding α-tropomyosin, collectively account for 10–15% of the cases [31-33]. Mutations in several other thin and thick filament proteins such as titin (*TTN*), cardiac α-actin (*ACTC1*) and essential and regulatory light chains (*MYL3* and *MYL2*, respectively) have also been reported but are infrequent [34]. The spectrum of the causal mutations in HCM was recently expanded to include mutations in the Z disk proteins *MYOZ2* and *TCAP*, encoding myozenin 2 (calsarcin 1) and telethonin, respectively [35••,36]. Mutations in *MYOZ2* and *TCAP* are rare causes of HCM. Except for the *MYBPC3* mutations, which encompass missense, insertion/deletion and splice junction mutations, the majority of the HCM mutations are missense mutations [31,32].

Several variants in genes coding for cardiac troponin C (*TNNC1*), α-MyHC (*MYH6*), myosin light chain kinase (*MYLK2*), phospholamban (*PLN*) and caveolin 3 (*CAV3*) have been identified in patients with HCM (Table 1) [34]. However, the causality remains to be established. It is also noteworthy that approximately 2% of patients with HCM may have two mutations in the sarcomeric proteins [37,38]. Collectively, the known causal genes and mutations account for approximately two-thirds of all HCM cases. The prevalence of the causal genes and mutations varies in different populations. In general, recurrent mutations are very uncommon, as each mutation is responsible for fewer than 1% of the HCM cases. Hence, HCM mutations are largely ‘private’ mutations.

It is also important to note that no protein is ‘perfect’. Accordingly, not every genetic variant, even if it leads to a change in the amino acid sequence or the predicted secondary structure of a protein, is a causal mutation. Sarcomeric proteins are no exception and contain nonsynonymous polymorphisms that do not cause a discernible clinical phenotype. This is illustrated for *TNNT2*, which contains the common R260K nonsynonymous change that is

present in various populations with an average heterozygosity of 0.14 single nucleotide polymorphism database (dbSNP). The frequency is much higher than the prevalence of HCM in humans, which is estimated at 1 in 500 [21]. Therefore, establishing the causality of genetic variants, particularly in the sporadic cases, mandates additional experiments.

Although HCM is considered a single disease entity, the genetic heterogeneity of HCM raises the possibility of the alternative. Functional studies point to the diversity of the effects of the causal mutations on protein and sarcomere structure and function. Likewise, cardiac hypertrophy is expected to involve a diverse array of signaling molecules, some of which could be gene-specific or mutation-specific. The point is supported by the identification of mutations in *MYOZ2*, which encode myozenin 2, an inhibitor of protein phosphatase calcineurin [35••]. We speculate that the pathogenesis of cardiac hypertrophy in HCM caused by the *MYOZ2* mutation involves activation of the calcineurin-signaling pathway. Accordingly, inhibition of calcineurin would be expected to reverse, attenuate or prevent cardiac hypertrophy in those with the *MYOZ2* mutations. In contrast to the anticipated effects in *MYOZ2* mutation carriers, treatment of the α-MyHC-Q403+/− mice with calcineurin inhibitors led to the deterioration of cardiac hypertrophy and function [39]. Likewise, the pathogenesis and specific treatment of HCM caused by mutations in *MYH7* and *TNNT2* are likely to differ significantly. For example, myofibrillar Ca^{2+} sensitivity for generation and ATPase activity are increased in mouse models of HCM caused by cardiac troponin T mutations, which is in contrast to those observed for the mutations in the β-MyHC [40,41]. Hence, one could speculate the possibility of gene-specific or pathway-specific treatment for reversal, attenuation and prevention of cardiac hypertrophy in HCM.

Cardiac hypertrophy in other genetic disorders

Cardiac hypertrophy is also a major phenotypic component of various genetic disorders such as storage diseases, triplet repeat syndromes and mitochondrial diseases. Often, the hypertrophic phenotype is indistinguishable from that of HCM caused by mutations in sarcomeric proteins, and hence they are clinically misdiagnosed as HCM. A typical example is cardiac hypertrophy in trinucleotide repeat syndromes, a class of neuromuscular disorders caused by the expansion of the trinucleotide repeats in various genes, such as myotonic muscular dystrophy or dystrophia myotonica (DM), Huntington's disease and fragile site syndromes [42]. The common form of dystrophia myotonica is caused by the expansion of naturally occurring GC-rich triplet repeats in the 3′ untranslated region of *DMPK*, which encodes dystrophia myotonica protein kinase. Cardiac hypertrophy, often diagnosed as HCM, and conduction defect are the prominent clinical features along with progressive degeneration of muscles and myotonia [43]. Cardiac hypertrophy or dilatation also occurs in patients with Friedreich's ataxia (FRDA), which is caused by the expansion of GAA repeat sequences in the *FRDA* gene [44]. Cardiac involvement is a major determinant of morbidity and mortality in triplet repeat syndromes [42,45]. The severity of clinical manifestations of triplet repeat syndromes correlates with the size of the repeats [46].

Cardiac hypertrophy, mimicking HCM, is also common in Noonan syndrome. Noonan syndrome is probably the most common cause of HCM phenocopy in children. The causal gene in approximately half of the cases is *PTPN11*, which encodes protein–tyrosine phosphatase, nonreceptor type 11 [47,48]. Other known causal genes are *SOS1*, *KRAS* and *RAF1*, which encode proteins involved in hypertrophic pathways [49•,50•,51].

Cardiac hypertrophy is a common feature of storage disorders such as Pompe disease (glycogen storage disease type II), which is an autosomal recessive disorder due to mutations in the gene encoding α-1,4-glucosidase (acid maltase) [52]. Likewise, mutations in the *PRKAG2* gene, which encodes the γ2 regulatory subunit of AMP-activated protein kinase (AMPK), cause

cardiac hypertrophy due to glycogen storage along with conduction defects and Wolff–Parkinson–White syndrome [53,54].

Cardiac hypertrophy is also a part of the phenotypic spectrum of mitochondrial DNA mutations [55]. Kearns–Sayre syndrome (KSS) is a mitochondrial disease that is often associated with cardiac hypertrophy. The typical phenotype of KSS includes a triad of progressive external ophthalmoplegia, pigmentary retinopathy, cardiac conduction defects and less commonly cardiac hypertrophy [56]. L-Carnitine deficiency, caused by mutations in chromosomal genes encoding solute carrier family 22, member 5 (*SLC22A5*) or OCTN2 transporter, could manifest as either concentric or eccentric cardiac hypertrophy [57]. Likewise, mutations in mitochondrial carnitine palmitoyltransferase I (*CATI*) and translocase (*SLC25A20*) are also associated with cardiac hypertrophy and heart failure. Moreover, mutations in acyl-CoA dehydrogenase could impair mitochondrial fatty acid oxidation and cause cardiac hypertrophy [57,58]. Cardiac hypertrophy has also been described in a variety of diseases such as mucopolysaccharidosis, Niemann–Pick disease, Gaucher disease, hereditary hemochromatosis, CD36 deficiency and Refsum disease [57].

Determinants of the phenotypic expression of cardiac hypertrophy

A diverse array of factors are expected to contribute to phenotypic expression of cardiac hypertrophy in HCM, including the causal genes, the modifier alleles, epigenetic factors, microRNAs, posttranslation protein modifications and environmental factors. The major determinants of cardiac hypertrophy in HCM are briefly discussed.

The causal mutations—The causal mutations are necessary and sufficient to induce cardiac hypertrophy in single-gene disorders. They probably are the most important determinant of the severity of the phenotype [30,59-63]. Most of the *MYH7* mutations are associated with an early onset and extensive cardiac hypertrophy [61,62,64,65]. In contrast, *MYBPC3* mutations cause less severe cardiac hypertrophy, which may develop later in life [22,30,62]. Likewise, most mutations in the components of the thin filaments, such as cTnT and cTnI, are associated with mild cardiac hypertrophy [59,66]. Notwithstanding this, however, there is considerable variability in the expression of cardiac hypertrophy even among individuals with identical causal mutations. The so-called ‘malignant’ or ‘benign’ phenotypes are not gene or even mutation-specific. Thus, the causal mutations are important, but only as partial determinants of the severity of cardiac hypertrophy.

The modifier genes—Modifier genes are referred to genes with sequence variants that affect phenotypic expression of the disease of interest. The distinction between causal and modifier genes is noteworthy. By definition, the causal genes are prerequisite and sufficient to cause the phenotype. However, they only partially determine the severity of the phenotype. Modifier genes or variants are neither necessary nor sufficient to cause the disease. However, the variants influence phenotypic expression of the disease, such as the degree of cardiac hypertrophy. The evidence for the presence of the modifier genes was strengthened upon identification of the causal mutations in families with HCM and detection of a considerable degree of variability in the clinical manifestations among family members. Likewise, the presence of phenotypic variability among individuals from different families with identical causal mutations further underscored the importance of the modifier genes. The interindividual variability in the expression of cardiac hypertrophy is partly due to the presence of considerable differences in the genomes of individuals. The most commonly recognized differences are the single nucleotide polymorphisms (SNPs). Likewise, there are abundant non-SNP and copy number variants (CNVs). The recent release of Dr J. Craig Venter’s genome sequence highlighted the presence of an enormous degree of variation, raising the possibility that each individual’s genome is indeed ‘private’ [67••]. Therefore, patients with HCM are expected to have

considerable differences in their genomic sequence, which could affect expression of cardiac hypertrophy.

The modifier genes for human HCM or cardiac hypertrophy are largely unknown. We recently mapped four modifier loci on 3q26.2 (180cM), 10p13 (41cM), 17q24 (108cM) and 16q12.2 (73cM) in a large family with HCM caused by the Ins791G mutation in *MYBPC3* [68••]. The effect size of the modifier loci ranged from approximately 8 g shift in left ventricular mass for 10p13 locus heterozygosity for the common allele to approximately 90 g for 3q26.2 locus homozygosity for the uncommon allele. Several studies (reviewed in [69]) have implicated the *ACE* gene encoding angiotensin-1 converting enzyme 1 and a few other genes as potential modifiers for HCM. Overall, a few modifier genes are expected to exert large effects, several moderate effects and the vast majority only modest effects on the phenotypic expression of HCM.

Other determinants of cardiac hypertrophy—Cardiac hypertrophy, whether due to a mutation in a single gene, such as that in HCM, or in acquired conditions such as valvular heart diseases, is a complex trait. The phenotype arises from complex interactions between the causal and modifier genes, environmental factors and the regulators of transcription and translation, including epigenetic factors, microRNAs and protein modifiers. Likewise, the composition of diet and physical exercise have been implicated in influencing expression of cardiac hypertrophy in mouse models [70,71]. Unfortunately, there is insufficient information on the effects of physical exercise and diet on the expression of pathological cardiac hypertrophy in humans. It is important to note that strenuous physical exercise is not recommended for those with pathological cardiac hypertrophy. It is noteworthy that HCM is the main cause of SCD in young competitive athletes, and death may occur during or immediately after exercise [23, 72].

Conclusion

Cardiac hypertrophy is a ubiquitous finding in various cardiovascular conditions and an important determinant of morbidity, mortality and the risk of SCD. Cardiac hypertrophy is a complex phenotype caused by the multifaceted interactions between a large array of genetic and nongenetic factors. Various trophic and mitotic agents and their receptors, signal transduction molecules and transcription factors are involved in the pathogenesis of cardiac hypertrophy. In addition to the causal genes, modifier genes also contribute significantly to expression of cardiac hypertrophy in single-gene disorders. Likewise, epigenetic factors, microRNAs and protein modifications such as phosphorylation, acetylation and glycation are expected to contribute to phenotypic expression of cardiac hypertrophy. Thus, to elucidate the pathogenesis of cardiac hypertrophy and deliver effective therapy, it is important to decipher the important determinants of the cardiac hypertrophic response.

Although HCM is clinically recognized as a single disease entity, molecular genetic and mechanistic studies point to the diversity of the pathways involved in its pathogenesis. The findings have raised the potential for specific therapies, designed and applied according to the specific causal genes and mutations. In addition, the elucidation of the molecular genetic basis of phenocopy states has exposed the limitations of the clinical diagnosis and emphasized the need to incorporate both a phenotype-based and a genotype-based diagnosis and treatment.

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References and recommended reading

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• of special interest

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 282).

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Table 1

Causal genes for hypertrophic cardiomyopathy

Gene	Symbol	Chromosome	Frequency
Established causal genes			
β-Myosin heavy chain	*MYH7*	14q1	~25–30%
Myosin binding protein-C	*MYBPC3*	11q1	~ 25–30%
Cardiac troponin T	*TNNT2*	1q3	~3–5%
Cardiac troponin I	*TNNI3*	19p13.2	~3–5%
α-Tropomyosin	*TPM1*	15q1	~1%
Myozenin 2	*MYOZ2*	4q25–26	1 : 250
Myosin light chain 1	*MYL3*	3p	Rare
Myosin light chain 2	*MYL2*	12q	Rare
α-Cardiac actin	*ACTC1*	15q11	Rare
Titin	*TTN*	2q13–33	Rare
Telethonin	*TCAP*	17q12	Rare
Possible causal genes			
Myosin light chain kinase 2	*MYLK2*	20q13.3	Rare
α-Myosin heavy chain	*MYH6*	14q12	Rare
Cardiac troponin C	*TNNC1*	3p21	Rare
Caveolin 3	*CAV3*	3p25	Rare
Phospholamban	*PLN*	6p22.1	Rare
Calreticulin	*CALR3*	19p13.11	Rare
Junctophilin-2	*JPH2*	20q13.12	Rare
Mitochondrial tRNAs	*MTTG, MTTI*	Mitochondrial DNA	Rare

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