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On Genetic and Phenotypic Variability of Hypertrophic Cardiomyopathy: Nature Versus Nurture*

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Abstract

The seminal discovery of the R403Q mutation in the beta-myosin heavy chain (MyHC) gene as a cause of hypertrophic cardiomyopathy (HCM) by Dr. Thierfelder's group a decade ago (1) ushered in a new era in the molecular genetics of HCM. To date, over 120 mutations in 10 genes, all encoding sarcomeric proteins, have been identified in patients with HCM (2), leading to the notion that HCM is a disease of contractile sarcomeric proteins (3). Mutations in nonsarcomeric genes, mitochondrial genome and genes responsible for the triplet repeat syndromes also have been found in patients with HCM (2). Although no large-scale systematic search has yet been performed, the existing data suggest that mutations in the beta-MyHC, myosin binding protein-C (MyBP-C) and cardiac troponin T (cTnT) are the most common causes of HCM, collectively accounting for approximately 60% to 70% of all HCM cases (2). It has also become evident that the frequency of each particular causal mutation in the HCM population is relatively low (<5%). Overall, genetic studies indicate significant allelic and nonallelic heterogeneity of HCM, an issue that complicates the feasibility of genetic diagnosis.

Identification of the causal mutations for HCM has afforded the opportunity to identify the genetic determinants of cardiac phenotypes, which are also known to be extremely variable. The results of several genotype-phenotype correlation studies suggest that mutations affect the phenotypic expression of HCM, particularly the magnitude of cardiac hypertrophy and the risk of sudden cardiac death (SCD). In general, HCM caused by mutations in the beta-MyHC appears at a younger age and is associated with more extensive hypertrophy and a higher incidence of SCD compared to HCM arising from mutations in the MyBP-C (4–7). The prognostic significance of the causal mutations is related to their influence on the magnitude of hypertrophy (8), perhaps with the exception of mutations in the cTnT, which often are associated with mild left ventricular hypertrophy but a relatively high incidence of SCD (9). However, the results of genotype-phenotype correlation studies in HCM have been confounded by the small size of the families, low frequency of each causal mutation, small number of families with identical mutations, variability of the phenotypic expression in affected individuals within the same family or among families with identical mutations and the effects of modifier genes and environmental factors. Thus, despite the initial enthusiasm regarding the clinical utility of the causal mutations as a means of identifying high risk subjects with HCM, it is evident that no particular clinical phenotype is mutation-specific. All in all, mutations exhibit highly variable clinical, electrocardiographic and echocardiographic manifestations.

In this issue of the *Journal*, Erdmann et al. (10) report on the frequency of mutations in the MyBP-C and the associated phenotypes in 110 genetically independent patients with HCM.

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They identified 13, including 11 novel mutations, in 15 index cases (14%). The spectrum of mutations included missense, nonsense, splice junction and small deletion/insertion mutations. Consistent with previous reports (5,6), left ventricular hypertrophy was relatively mild and the clinical features were diverse. Premature SCD, myomectomy to relieve outflow tract gradients, and implantation of defibrillator for sustained ventricular arrhythmias were also observed and were more common in those patients with the deletion or truncation mutations. The findings of Erdmann et al. (10) further illustrate the genetic and clinical heterogeneity of HCM caused by mutations in MyBP-C. The frequency of the observed MyBP-C mutations is subject to the sensitivity of the screening technique, comprehensiveness of the screening procedure and selection of the population. Erdmann et al. (10) used single stranded conformational polymorphism (SSCP) as the screening technique, which has a sensitivity of approximately 70% to 80%. In addition, restriction of screening to the coding and adjacent sequences, although justified and a common practice, would not allow for detection of mutations that are located in the regulatory sequences.

Characteristics of the study population are perhaps the most important determinants of the results of mutational screening studies. An important feature of HCM and other autosomal dominant diseases is the age-dependent penetrance of the causal mutations, which is also documented for the MyBP-C mutations in another study in this issue of the *Journal* (11). Screening of the index cases with established clinical phenotypes in early life will lead to underestimation of the frequency of the mutations that are associated with a low penetrance. In contrast, screening of elderly subjects with established phenotypes could lead to underestimation of the true prevalence of mutations that confer a survival disadvantage, and thus, those associated with a benign prognosis will be over-represented. The relatively young age of the 110 index cases in the present study along with the use of SSCP for mutation detection are likely to lead to underestimation of the true prevalence of MyBP-C mutations in the general population of HCM. Determination of the true prevalence of each particular causal gene and mutation for HCM requires large-scale epidemiologic studies in the general population without considering the presence or absence of the clinical phenotype. Collectively, based on the previous data (5,6) and the report by Erdmann et al. (10) it is reasonable to estimate that mutations in the MyBP-C account for approximately 20% to 25% of all HCM cases.

Over 40 different mutations in the *MYBPC3* gene, which codes for the MyBP-C protein, have been identified in patients with HCM. As is the case for mutations in other causal genes for HCM, no particular MyBP-C mutation predominates, and the frequency of each mutation is low. The existing data suggest that the vast majority of the mutations in HCM arise independently. Thus, a founder effect (common ancestor) is unusual. An intriguing feature of mutations in the *MYBPC3* gene is their spectrum, which comprise not only missense mutations but also deletion/insertion and splice junction mutations (5,7,12). This is unlike mutations in the beta-MyHC or cTnT, which are predominantly missense mutations. Deletion/insertion mutations are expected to result in frame-shift or truncation of the MyBP-C proteins, leading either to severe structural and functional defects in the protein or to immediate degradation of the expressed protein. The basis for the relative preponderance of the frame-shift and truncation mutations in the MyBP-C protein is unknown, possibly reflecting the complexity of the gene structure.

Alternatively, one might speculate that mutations, whether missense or insertion/deletion, occur randomly, irrespective of the causal genes. However, survival of the mutation carriers varies according to the functional and structural significance of the causal gene. Frame-shift or deletion mutations in the beta-MyHC or cTnT that cause major structural and functional changes in the protein could induce an early embryonic death. In contrast, similar mutations in proteins that have lesser roles in sarcomere structure and function could be compatible with survival and, thus will be found in patients with HCM.

A characteristic feature of human HCM, like all other autosomal dominant diseases, is the presence of significant variability in its phenotypic expression, such as cardiac hypertrophy and SCD. Factors that account for the variability of cardiac phenotypes are largely unknown. Diversity of the causal genes and mutations are partly responsible; but modifier genes and environmental factors also affect the phenotypic expression of HCM. Mutations in the MyBP-C are generally associated with a relatively mild cardiac hypertrophy and a low incidence of SCD as compared to mutations in the beta-MyHC (5,6). However, as shown by Erdmann et al. (10), malignant features such as SCD, sustained ventricular tachycardia and severe hypertrophy also occur. The investigators (10) suggest that severe phenotypes were more frequent in subjects with the frame-shift and deletion mutations, which are expected to alter the structure of the MyBP-C protein drastically. However, the sample size and the number of events were relatively small to draw firm conclusions. In addition, this observation is in contrast to a previous report showing a higher survival rate in subjects with deletion mutations (5). As stated earlier, multiple confounding factors limit the overall utility of the genotype-phenotype correlation studies in HCM, thus emphasizing the need for large-scale studies. Hence, comprehensive clinical data in conjunction with the genetic information should be combined when providing counseling to subjects with HCM.

Like all other autosomal dominant diseases, penetrance of the causal mutations in HCM (for clinical phenotypes) is also age-dependent. Causal mutations, present at birth, do not lead to hypertrophy and other clinical phenotypes often until the third and fourth decades of life. Penetrance is partially mutation-dependent and is relatively low for mutations in the MyBP-C (5,6). Therefore, absence of cardiac hypertrophy in members of families with HCM in the early decades of life does not exclude the possibility of development of HCM later in life. In this issue of the *Journal*, Maron et al. (11) demonstrate this point for mutations in the MyBP-C by documenting the evolution of cardiac hypertrophy in subjects who had no hypertrophy on the initial echocardiograms performed earlier in life. The relatively low sensitivity of echocardiographic findings of cardiac hypertrophy for early detection of mutation carriers in HCM is in accord with the current hypothesis that hypertrophy is a “compensatory” phenotype secondary to functional and molecular phenotypes (13). Accordingly, a functional phenotype is expected to be more sensitive in identification of mutation carriers than a structural phenotype, such as cardiac hypertrophy. In support of this notion, we have shown, in a transgenic rabbit model that fully recapitulates the phenotype of human HCM (14), that reduced myocardial Doppler velocities identified all mutation carriers even in the absence of cardiac hypertrophy (15). Thus, we proposed that tissue Doppler imaging, which detects myocardial contraction and relaxation abnormalities, could be used for early detection of mutation carriers in human subjects prior to the development of and independent of cardiac hypertrophy.

The basis for the age-dependent penetrance of mutations responsible for autosomal dominant diseases, such as HCM, and the reasons for the variations in the penetrance among subjects with identical mutations or mutation carriers within a family remain unknown. An attractive hypothesis is the possible role of mutations in the mitochondrial genome and reactive oxygen species (ROS). An age-dependent increase in mitochondrial DNA mutations could lead to an increase in the production of ROS, which are known to exert a diverse array of biologic functions including activation of hypertrophic signals. Despite the plausibility of the role of ROS in induction of an age-dependent cardiac hypertrophic response, their function in modulating cardiac phenotypes in HCM is speculative.

Genetic factors other than the causal mutations, referred to as the *modifier genes* or the *genetic background*, affect the phenotypic expression of HCM. Thus, although HCM is a classic example of a “monogenic” disorder, it is not, in a sense, purely “monogenic” because expression of multiple genes affects its phenotype. Causal mutations in the contractile sarcomeric proteins are necessary for the development of HCM and contribute significantly to

its phenotypic expression. In contrast, modifier genes that are neither necessary nor sufficient to cause HCM affect the severity of cardiac phenotypes. The final phenotype is the product of the causal mutations, modifier genes and environmental factors. The identity of the modifier genes for HCM and the magnitude of their effects have not been systematically explored. Because of the complexity of the molecular biology of cardiac hypertrophy, a large number of genes are likely to modify expression of cardiac phenotypes in HCM, each exerting a modest effect. In addition, complex genotype-genotype and genotype-environment interactions could influence the phenotypic expression of HCM. It is estimated that the human genome, comprised of approximately 30,000 to 50,000 genes, contains 2.1 million single nucleotide polymorphisms (SNPs). Approximately 100,000 are likely to affect expression levels or structure of the encoded proteins, and thus exert biologic effects. Based on the results of simple polymorphism association studies, several potential modifier genes have been identified including the gene encoding angiotensin-1-converting enzyme-1 (16–18). Because of the limitations of association studies and the allelic and nonallelic heterogeneity of HCM, large-scale systematic studies are needed to identify the modifier genes for HCM.

The mechanisms by which mutations in the MyBP-C protein lead to HCM are largely unknown. The MyBP-C protein is both a functional and a structural component of the sarcomere (19). It participates in sarcomere assembly through binding with other sarcomeric proteins. The last 102 amino acids of MyBP-C bind to the rod and subfragment-2 regions of MyHC in the A band of the sarcomere. The MyBP-C protein also binds to titin, a giant protein that spans the length of the sarcomere at multiple and regular intervals. Binding of MyBP-C to MyHC and titin provides stability to sarcomere organization. Also, MyBP-C modulates cardiac contraction by regulating actin-activated ATPase activity of the MyHC protein. Cardiac MyBP-C possesses at least three phosphorylation sites that are located between amino acids 157 to 259 and are amenable to phosphorylation by cAMP-dependent-and calcium/calmodulin-dependent protein kinases (19). Phosphorylation of the cardiac-specific domain in response to adrenergic stimulation modulates cardiac contractility. Mutations in the MyBP-C commonly affect the functional domains of the MyBP-C, including its binding sites for MyHC and titin (5,6). The primary defect caused by mutations in the MyBP-C is likely to be diverse and differ for missense, frame-shift and truncation mutations. The MyBP-C proteins carrying the missense mutations could incorporate into myofibrils but cause myocyte mechanical dysfunction and impair generation of the contractile force. Insertion/deletion mutations could lead to expression of truncated proteins that degrade immediately and cause haplo-insufficiency, or do not properly incorporate into sarcomere and cause sarcomere dysgenesis. Thus, mutations in the MyBP-C could affect orderly formation of thick filaments and/or alter cardiac myocyte mechanical function, particularly in response to adrenergic stimulation. Overall, the expected functional defect conferred by mutations in the MyBP-C is impaired generation of force of contraction by the cardiac myocytes, which could lead to increased myocyte stress and subsequent activation of stress-responsive signaling kinases and increased expression of trophic and mitotic factors in the heart (13). Activation of signaling kinases and increased expression of trophic factors lead to activation of the transcriptional machinery, increased gene expression and induction of hypertrophy, disarray, fibrosis and other histologic and clinical phenotypes of HCM.

In conclusion, humans with HCM exhibit a variety of phenotypes. The variability is due to the diversity of the causal genes and mutations and effects of the modifier genes and environmental factors. Large-scale genetic epidemiologic studies are necessary to determine the true frequency of the causal genes and mutations, to identify the modifier genes and to determine the magnitude of their effects and the effects of environmental factors on the phenotypic expression of HCM. Elucidation of the molecular bases for the diversity of cardiac phenotypes could lead to more accurate diagnosis, risk stratification and management of patients with HCM.

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