Hypertrophic cardiomyopathy (HCM) is a common inherited disorder with an estimated prevalence of ≥1 in 500 worldwide. The disease is inherited in families in an autosomal dominant fashion and is usually caused by mutations in genes encoding contractile proteins such as cardiac β-myosin heavy chain (MYH7), cardiac troponin T (TNNT2), cardiac myosin binding protein-C (MYBPC3), cardiac troponin I, α-myosin heavy chain, cardiac α-actin, α-tropomyosin, titin, myosin regulatory light chain, and myosin essential light chain. Several HCM disease genes remain to be identified.

The most obvious clinical manifestation of HCM is left ventricular hypertrophy. Although such hypertrophy is classically asymmetrical with prominent involvement of the interventricular septum, both concentric and apical hypertrophy can also occur. In fact, affected individuals may not exhibit any hypertrophy. Other clinical features are similarly variable in their expression and include sudden cardiac death, heart failure, arrhythmias, stroke, heart block, and infective endocarditis. Some patients remain asymptomatic throughout their lifetime. Many HCM patients have no or only minor symptoms, and asymptomatic affected children and adolescents are often diagnosed during family screening after another family member comes to medical attention.1 The average annual risk of sudden cardiac death in a HCM patient is 1%;2 and in high risk patients, prophylactic defibrillator implantation can be lifesaving.

Given marked variation in penetrance and expressivity, early diagnosis and reliable prognostic tools are crucial for primary prevention and proper followup of affected individuals and their family members. Current guidelines recommend that all first-degree relatives of an individual affected by HCM should be clinically evaluated by history, physical examination, electrocardiography, and echocardiography. With increased understanding of the molecular genetic causes of HCM and advances in modern laboratory technology, clinical genetic testing for HCM has become increasingly feasible.3 The GeneTests database (http://www.ncbi.nlm.nih.gov/sites/GeneTests) currently lists 5 US clinical laboratories offering some form of HCM genetic testing, as well as 7 additional European clinical laboratories.

However, a role of clinical genetic testing for HCM has not been well defined.

The 2003 American College of Cardiology-European Society of Cardiology Task Force on HCM3 noted that obstacles to routine deployment of HCM genetic testing include the marked intergenic and intragenic heterogeneity of the disorder as well as expensive and complex technological barriers to efficient screening of at least 10 different causal genes in any given proband. Although costs of sequencing and mutational analyses have markedly decreased since then, the price of testing generally remains in the thousands of dollars, and genetic heterogeneity remains a persistent challenge. Thus, HCM genetic testing has remained a mainstay of evaluation of families with a previously identified gene mutation rather than a screening tool for the general population. Using genetic testing in HCM families acknowledges that first degree relatives generally have a 50% risk of sharing disease causing mutations, and all relatives found to carry such a mutation (even if they do not initially manifest any clinical signs or symptoms of HCM) should have annual surveillance evaluations including resting and ambulatory ECG, echocardiography, and exercise testing to assess progression of hypertrophy and sudden cardiac death risk.

However, even when an HCM causing mutation has been identified, it is challenging to use the genotype to predict an individual patient’s clinical course. In some cases, unrelated families with the same sarcomeric gene mutation have been identified, but prognosis and severity has been dramatically different. Such seeming paradoxes are likely consequences of extensive modifying effects of as yet unidentified genetic factors as well as impact of poorly understood environmental factors such as diet.1 However, the greater challenge to establishing genotype/phenotype correlations has been the extensive frequency of “private” mutations. The Partners Healthcare Center for Personalized Genetic Medicine has found in their clinical testing program that approximately two-thirds of the HCM mutations identified among more than 2000 probands occur in only one family (H. Rhein, personal communication).

However, some genetic variants do represent mutational “hotspots.” In this issue of Circulation Research, Saltzman et al4 provide intriguing findings regarding one relatively common recurring HCM mutation. They report about significance of the Arg502Trp MYBPC3 variant in 1414 unrelated white HCM patients. It is generally accepted that the most common genetic causes of HCM are mutations in MYH7, TNNT2, and MYBPC3, and, combined, mutations in these 3 genes account for approximately half of HCM. Up to one-fourth of patients have MYBPC3 mutations, and mutations in this gene account for 40% to 48% of HCM causing mutations that have been
identified. A broad range of MYBPC3 gene defects, including missense, nonsense, splicing, deletion, and insertion mutations, have been identified. Earlier reports have suggested that the prognosis of MYBPC3 mutations is better than that associated with mutations in other sarcomeric genes such as MYH7 or TNNT2, but contradictory findings have also been reported, and each study has analyzed at most a few hundred patients. Differing prognoses have also been observed with different MYBPC3 mutation classes, and protein-truncating mutations have been suggested to be associated with more severe disease phenotypes than MYBPC3 missense or deletion mutations. Approximately 40% of adults with MYBPC3 mutations do not display cardiac hypertrophy before age 50, and disease penetrance may remain incomplete through age 60.

The Arg502Trp MYBPC3 variant has been identified in several independent analyses, although the population frequency of the mutation is not clear from these studies. However, Saltzman et al. show that this variant is the most common cause of HCM in their large study cohort and accounts for 2.4% of HCM. Saltzman et al. confirm that, in these probands and their affected family members, HCM associated with MYBPC3 Arg502Trp exhibits a delayed age of diagnosis compared with at least one MYH7 mutation (Arg719Trp), but the authors show that this aspect of MYBPC3 Arg502Trp was not different from MYBPC3 truncating mutations. More importantly, the prognosis conferred by MYBPC3 Arg502Trp was better than that associated with MYBPC3-truncating mutations or several MYH7 mutations. However, little comfort is offered here to patients with MYBPC3 Arg502Trp because the more “benign” prognosis still equated to nearly one-third of carriers developing adverse cardiac events (sudden cardiac death, implantable cardioverter defibrillator implantation, transplant, or myocarditis) by age 50, and 10% having such events by age 20. Moreover, several individuals carried both MYBPC3 Arg502Trp, as well as other mutations in another sarcomeric gene, and the combination of these mutations carries an even worse prognosis with three-fourths of such individuals having an adverse cardiac event by age 20.

This new study of a community-based large cohort highlights grim news for individuals with HCM given the significant risk of adverse events for patients with a presumed “benign” mutation, but it remains to be determined how these findings might impact on patient care. Certainly, physicians would appreciate an opportunity to discriminate low-risk patients from those with poor prognosis and to more rationally deploy prophylactic pharmacological therapy to prevent remodeling as well as implantable cardioverter defibrillator implantation to prevent sudden cardiac death. Unfortunately, these new data seem to provide subsets among patients at significant risk for poor outcomes rather than highlighting a patient group with a truly benign prognosis in whom one might defer interventions. Nevertheless, such studies provide an important template for investigators to try to establish such risk stratification. They highlight that clinically important information can potentially be gleaned from the one-third of HCM probands who, in fact, do have shared, nonprivate gene mutations. Moreover, we are reminded of the importance of evaluating genotype/phenotype correlations in large populations derived from community-based clinical genetic testing programs that avoid the biases incurred by populations selected by single highly specialized research laboratories. The contradictions in previous reports about severity of MYBPC3-related HCM may actually be more apparent than real; they may reflect differential aggregation in small cohorts of several unique HCM mutations with varying degrees of clinical consequence.

Future studies that examine genotype/phenotype correlations will also need to be inclusive of diverse populations. The impact of MYBPC3 Arg502Trp in the setting of nonwhite genetic backgrounds is, as yet, unknown. Moreover, distinct mutational hotspots are likely to play critical roles in HCM onset and progression in other races and ethnicities. For instance, a 25-bp deletion in MYBPC3 has been proposed to occur in 2% to 8% of a South Asian populations but was not recognized in other regions. Interestingly, however, analyses of phenotypic consequences of this MYBPC3 deletion were similar to that of MYBPC3 Arg502Trp. By itself, the MYBPC3 deletion had reduced penetrance and expressivity but had more severe and earlier disease manifestations in individuals who carried 2 sarcomeric gene mutations, ie, homozygotes for the MYBPC3 deletion or compound heterozygotes for both the MYBPC3 deletion and a deletion mutation in MYH7.

It has been 20 years since Seidman and colleagues identified the first molecular genetic cause of HCM, and the intervening decades have brought major advances in both our understanding of HCM pathogenesis and our strategies for diagnosis and treatment. We continue to evolve new diagnostic strategies, such as tissue Doppler echocardiography and MRI, to identify affected individuals earlier and with greater accuracy. However, our ability to determine the patients who most need our attention in this common disorder remains limited. As we deploy clinical genetic testing for HCM in concert with advanced imaging modalities, we will now be able to discern more precise genotype-phenotype correlations. In turn, we will develop better predictors of risk and select the best arrows from our medical quiver to target the adversity faced by HCM patients.

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