A Paradigm Shift in Our Understanding of the Development of the Hypertrophic Cardiomyopathy Phenotype? Not So Fast!

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It has now been more than 2 decades since the seminal observation that hypertrophic cardiomyopathy (HCM) is caused by mutations encoding for the contractile proteins of the cardiac sarcomere.1 Over this relatively short period of time, our understanding of the molecular basis of this disease has grown enormously, including the identification now of >1400 individual mutations (in at least 11 different sarcomere genes) associated with HCM.2–8 This genetic heterogeneity is undoubtedly responsible for the diverse phenotypic expression and natural history observed within HCM.4,9,10 However, from a clinical perspective, perhaps the most important advance to have emerged from the current molecular era is automated DNA sequencing, which has led directly to the development of comprehensive genetic testing panels which identify mutations responsible for HCM.5–8

The powerful clinical application for genetic testing has provided the opportunity for family screening and diagnosis.6–8,11,12 If a disease-causing sarcomere mutation can be identified in the affected proband, relatives can then be genetically tested to determine whether they have the same mutation, and as a consequence whether they are at risk of developing disease. If such relatives do not carry the mutation there is virtually no future risk of developing HCM, and no further screening is necessary.5–8 This information can have a positive impact on HCM family members, lifting the substantial psychological burden often created by the possibility of transmitting a genetic heart disease, as well as the chance to eliminate the need for additional testing and the cost-burden associated with screening. However, it should be underscored that this strategy is predicated on the ability to identify a pathogenic mutation in the proband, a potential limitation because <50% of the time will genetic testing panels identify a mutation which can then be used to reliably test other family members.5,7

Genetic testing has also led to identification of HCM family members who carry a disease-causing sarcomere mutation without left ventricular (LV) hypertrophy (ie, genotype-positive/phenotype-negative), but who are nevertheless at risk of developing clinical disease in the future.5,10,12 The majority of these predominantly asymptomatic patients are recognized at a young age (<18 years of age). The increasing number of genotype-positive/phenotype-negative patients now being identified has raised a number of clinical dilemmas, including decisions regarding recommendations for participation in competitive sports, which remains unresolved and should be decided on a case-by-case basis. In addition, even after >50 years of studying HCM, the risk of eventually developing LV hypertrophy, and the age at which phenotypic conversion will occur (if even at all), still remain unknown.12

There are a number of reasons why this is the case, including the following: (1) the denominator of HCM relatives at risk for developing disease is not known, because of the relatively short period of time that genetic testing has been available for family testing; (2) pathogenic mutations can be identified in only a limited number of affected probands.5–7 dramatically reducing the denominator of potential genotype-positive at-risk family members who can be prospectively followed for disease development; (3) HCM phenotypic conversion can occur at any age throughout life,15–17 which means that substantial duration of follow-up is necessary to clarify penetrance in this disease. Indeed, delayed phenotypic expression into the third or fourth decades of life (or even later) is known to occur, but is likely uncommon.15–17 Nevertheless, the paradigm governing the HCM phenotype, established over the last 40 years and based predominantly on cross-sectional clinical studies, has been that most relatives who inherit a disease-causing mutation will show evidence of LV hypertrophy during childhood and adolescence.10 Increases in LV wall thickness are usually complete on achieving physical maturity (ie, ≈20 years of age). In this edition of Circulation, Jensen and colleagues18 have reported the results of a genetic testing strategy conducted in a cohort of HCM families to determine the penetrance of the HCM phenotype (ie, LV hypertrophy). The authors report the longitudinal follow-up of 12 children identified with a disease-causing sarcomere mutation from several genotyped HCM families (MYH7 and MYBPC3, the 2 most common genes in HCM). Among these genetically affected patients, 3 were only 13, 17, and 19 years of age at the end of follow-up, whereas the remaining 9 were clinically followed beyond adolescences through to early adulthood (up to 28 years of age). Of these 9, 2 developed LV hypertrophy at 26 and 28 years of age.

In addition, another subgroup of 24 child relatives without LV hypertrophy from HCM families was also identified as...
part of the study. Although considered at risk for developing HCM by virtue of being related to the proband, their genetic status was unknown, and therefore these subjects cannot be used to determine disease penetrance.

However, questions regarding future risk of developing HCM arise commonly in the clinic from concerned patients and family members. In this regard, these data, together with the only other longitudinal study to follow at-risk HCM patients for development of LV hypertrophy, would suggest that the incidence of developing the HCM phenotype during childhood and adolescence may be lower than previously considered. Although this may provide some limited information for physicians to provide relatives at risk for HCM, these observations are still based on very small numbers of patients.

These data of Jensen et al do confirm the previously reported principle of late-onset phenotypic development in HCM, based on their 2 patients who developed mild LV wall thickening at ages 26 and 28. Indeed, the frequency at which delayed phenotypic expression occurs in HCM is at this time not known. This is because the opportunity to document these events with serial imaging studies (particularly during midlife and beyond) is uncommon, and when it occurs recognition is usually under fortuitous circumstances. In addition, in the future it will be extremely difficult (if not impossible) to ascertain the precise prevalence of late-onset disease because known genetically-affected family members would have to be followed with serial imaging over decades.

So then, what data are available to support the principle that LV remodeling can begin later in life? A small number of anecdotal cases using serial imaging with echocardiography and CMR have demonstrated convincingly that the phenomenon of late-onset hypertrophy does occur. The majority of these cases appear to happen in the 3rd or 4th decade of life, although a recent report has demonstrated phenotypic conversion occurring after 40 years of age in 4 patients, including 1 patient after 70 years of age. The totality of these observations, small in number as they are, suggests that in HCM a remodeling process resulting in increased LV wall thickness can develop at virtually any age. As a result, relatives who are identified with an HCM disease-causing mutation should be informed that risk for developing clinical disease can extend well beyond adolescence, with no apparent age to which immunity for phenotypic conversion exists.

For these reasons, it is important to underscore that the available observations concerning delayed-onset phenotypic development support the current screening guidelines for HCM, which already take into account this important disease-related principle. For HCM family members who have achieved adulthood without LV hypertrophy, the period of echocardiographic and possibly CMR imaging should be extended and performed about every 5 years until at least midlife. The decision to continue screening beyond this point should be determined on an individual patient basis, depending on the clinical scenario or if symptoms occur suspicious for HCM.

A major inference of the data of Jensen et al is that the majority of genetically-affected relatives in HCM families do not develop LV hypertrophy during childhood and adolescence but rather much later in adulthood (or never). Importantly, this principle is based on a small, select cohort of <10 genetically-affected patients. In contrast, over the last 40 years clinicians have evaluated thousands of HCM patients with LV hypertrophy, including a substantial proportion aged <20 years, many of whom have documented sarcomere mutations. Even before the echocardiographic era, Dr Eugene Braunwald’s initial clinical report of the first 64 HCM patients identified with LV hypertrophy by angiography included one-third who were children or adolescents. Furthermore, in the early echocardiographic era of the 1980s, studies demonstrated the development and progression of LV hypertrophy in young HCM patients. Since then studies too numerous to cite here have included a multitude of young HCM patients with LV hypertrophy as their diagnostic marker. Finally, forensic databases in the United States have documented HCM as the most common cause of sudden death in young competitive athletes, responsible for about one-third of all athletic field deaths.

Therefore, it would seem implausible that all HCM patients who come to clinical recognition in their 3rd or 4th decade of life represent late-onset disease expression. In addition, we cannot exclude the possibility that the unique genetic substrate derived from this relatively homogenous population may not reflect that of HCM at large. Therefore, promoting a paradigm shift in HCM phenotypic development based on the observations of only a small number of genotype-positive/pheno

type-negative HCM patients, while overlooking the thousands of young HCM patients with LV hypertrophy who have been identified and reported over the last half century of investigation in this disease, seems unlikely.

Finally, the emerging contemporary imaging era of HCM emphasizes important limitations in studying the HCM phenotype by echocardiography alone. Over the last 10 years, CMR with its high spatial resolution and tomographic imaging capability has emerged as a technique particularly well-suited to characterize the diverse phenotypic expression of this complex disease. For example, CMR is often superior to echocardiography for HCM diagnosis, by identifying areas of segmental hypertrophy (ie, anterolateral wall or apex) not reliably visualized by echocardiography as well as other high-risk HCM patient subgroups, including those with thin-walled scarred LV apical aneurysms. Therefore, without CMR it is not possible to be absolutely sure that young relatives in HCM families are truly phenotype-negative.

Jensen et al provide one of the very few longitudinal follow-up studies offering insight into what information physicians can tell HCM relatives about the possibility of phenotypic conversion, while also reaffirming the principle of late-onset disease development and the need for prolonged screening among at-risk family members. On the other hand, this study also highlights the enormous challenges involved in defining more precisely the HCM phenotype as it develops throughout life, but based on the study design cannot completely change the way we currently view HCM phenotypic development. However, these data should act as a call to arms to encourage future investigation in this largely overlooked area of HCM study through the development of robust databases aimed to more precisely define the complexities of the evolution of LV hypertrophy in this disease.
Disclosures
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References

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