Phenotype–Genotype Correlation in Hypertrophic Cardiomyopathy

Less Signal, More Noise?

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Identification of a genetic basis for hypertrophic cardiomyopathy (HCM) has proven to be more complex than originally postulated. Early reports in the 1950s and 1960s of clusters of patients within families with left ventricular hypertrophy (LVH), cardiac myocyte disarray, and fibrosis, as well as symptoms of heart failure and sudden cardiac death, with what seemed to be caused by an autosomal dominant pattern of inheritance, led to initial excitement regarding genetic testing in the 1990s.[1] Although initial attempts to identify candidate genes led to the seminal discoveries of discrete mutations in the MYH7 (β-myosin heavy chain), which segregated within affected individuals in families,[2] these mutations were not present in all families with HCM. Further analysis of affected families led to the identification of mutations in genes for other sarcomere proteins including other thick filaments (MYL2 [regulatory myosin light chain] and MYL3 [essential myosin light chain]), thin filaments (TNNT2 [cardiac troponin T], TNNI3 [cardiac troponin I], TNNC1 [cardiac troponin C], TPM-1 [α-tropomyosin], and ACTA [α-cardiac actin]), MYBPC3 (cardiac myosin-binding protein c), and z-disc proteins (ACTN2 [α-actinin 2] and MYOZ2 [myozenin 2]).[1] At this point, >1400 mutations in 11 sarcomere protein genes have been identified, although ≈50% of identified mutations are in MYH7 or MYBPC3.[3] Although the majority of mutations are private mutations within a family or as a de novo mutations, there are some HCM gene mutations referred to as founder mutations, which are highly conserved within populations that often have been historically geographically or culturally isolated. These occur almost exclusively in the MYBPC3 gene resulting in a truncated protein and delayed penetrance until after the reproductive years.[1,4] At present, genetic testing identifies a known pathogenic or presumed pathogenic mutation in ≈30% to 40% of patients with phenotypic HCM. Both the Toronto Genotype score and Mayo HCM Genotype Predictor scores were developed as tools for clinicians with a way to identify patients with the highest likelihood for positive genetic testing based on clinical characteristics such as age of diagnosis, left ventricular (LV) morphological subtype, LV wall thickness, and a family history of HCM.[5,6]

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However, despite improved genetic testing, there remains much to be discovered about the genetic, epigenetic, and environmental factors that influence phenotype in HCM.[7] Initial reports on specific families were thought to be promising for linking specific gene mutations to phenotypic expression. For instance, the Arg453Cys mutation in MYH7 has been associated with a high incidence of end-stage heart failure and premature death.[8] Subsequent studies found that patients with genetic mutations have an earlier onset of disease, more severe LVH, and a family history of HCM or sudden cardiac death compared with genotype-negative patients with HCM.[9] Additionally, the observation that ≈5% to 7% of patients with HCM will have ≥2 mutations and that these patients tend to have a more severe phenotype has given credence to the gene-dose theory.[4] Although most patients are heterozygous for a particular mutation, those who are homozygous tend to have a more severe phenotype as well. For example, the 3330+2T>G mutation on the MYBPC3 gene within the Old Order Amish community has been documented to be associated with a lethal infantile form of HCM when patients are homozygous for the mutation.[10] Although these investigations on specific mutations have hinted toward specific associated phenotypes, they were often conducted within a family or small number of families to which the mutation has been limited.

Studies of larger families with the same gene mutation have shown penetrance to be ≈60% with symptoms ranging from asymptomatic to sudden death, and with varying patterns of LVH, making the utility of gene testing to predict prognosis and degree of gene penetrance less effective.[11] Variable penetrance has led to the discovery of modifier genes, like angiotensin-converting enzyme-1, endothelin-1, and tumor necrosis factor-α, or environmental factors like hypertension alter the phenotype, further complicating genotype–phenotype correlations. However, although hypertension and modifier genes add to the complexity of phenotypic expression, they do provide a potentially modifiable substrate to lessen hypertrophy and fibrosis in patients with HCM.

Recognizing the significant degree of heterogeneity in genetic mutations in HCM, more recent studies have sought to identify phenotypes associated with mutations to a gene instead of the exact mutation. Unfortunately, comparisons of mutations to a specific gene to another, for instance MYBPC3 to MYH7, have not yielded significant differences

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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The views in the editorial are those of the authors and do not reflect that of the National Institutes of Health or other coinvestigators of the HCMR (Hypertrophic Cardiomyopathy Registry) trial.

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(*Circ Cardiovasc Imaging*. 2017;10:e006066. DOI: 10.1161/CIRCIMAGING.117.006066.)

***Circ Cardiovasc Imaging* is available at http://circimaging.ahajournals.org**
DOI: 10.1161/CIRCIMAGING.117.006066

in phenotype either.[9] Woo et al[12] theorized that mutations correlating to functional domains of the proteins encoded by the gene may affect phenotype. They examined 74 patients with mutations in the MYH7 gene (β-myosin heavy chain) and found that prognosis correlated with the affected functional domain of MYH7 and specifically that patients with mutations in the ATP hydrolysis active site and the rod portion had decreased survival. Although this study was small and limited to mutations in one gene (MYH7), it suggests another framework in which to analyze the extensive data on genotype and phenotype in HCM.

In this issue of *Circulation: Cardiovascular Imaging*, Weissler-Snir et al[13] provide further evidence that although our understanding of this disease is growing, we still have much to learn about the disease process and its complex genetics. Accordingly, the authors sought to evaluate only those patients with phenotypic HCM with a single pathogenic or presumed pathogenic mutation in either MYBPC3 or MYH7. This was designed to increase the probability to detect differences in phenotype but avoided including patients with multiple mutations who have previously been shown to have a more severe phenotype. Importantly, this study included 159 patients with phenotypic HCM and a single mutation, which is one of the largest cohorts studied and certainly the largest genotype-positive cohort by cardiac magnetic resonance (CMR) imaging. Similar to previous studies, there was significant variation within the mutations reported per gene; 46 different mutations in 75 patients with MYBPC3 mutations, 33 different mutations in 53 patients with MYH7 mutations, and 18 different mutations in 31 patients with thin-filament (tropomyosin, actin, myosin light chain, and troponin t, I, and c) mutations. In their comparison of baseline characteristics and CMR imaging findings, there was no significant difference between breakdown of New York Heart Association functional class, presence of LV outflow tract obstruction, risk factors for sudden death, LV chamber dimensions, LVH morphology, presence or degree of late gadolinium enhancement (LGE), or mitral leaflet length. In terms of limitation, follow-up was of relatively short duration, and in this setting, the authors did not find significant differences in outcomes (sudden cardiac death, septal reduction therapy, left ventricular ejection fraction <50%, or atrial fibrillation) between the MYH7 and MYBPC3 groups. Although they report increased prevalence of LV outflow tract obstruction and family history of sudden cardiac death, lower left ventricular ejection fraction, and increased LV systolic volumes for patients with thin-filament mutations, these encompass 18 different mutations in 7 different genes in 31 patients, which makes it difficult to interpret whether this finding is by chance, truly generalizable to mutations in thin filaments, or whether this may be attributable to a specific thin filament. This will need to be further studied in ongoing investigations.

Their data confirm findings of previous studies examining differences in phenotypes in patients with MYH7 and MYBPC3 mutations. The majority of previous studies in genotype-positive HCM patients examining phenotype used echocardiography instead of CMR imaging. CMR imaging allows for more precise evaluation of mitral valve papillary muscle morphology, quantification of LV mass, and identification of LGE, as well as exploration of T1 times to assess extracellular volume, whereas because of superior temporal resolution, mitral valve leaflets, and chordal attachment and motion are better seen by echocardiography.[14] As the authors pointed out in the discussion, previous studies evaluating CMR imaging, genotype, and phenotype in patients with genotype-positive HCM have been small. Predominant findings have been that LGE is more prevalent in genotype-positive HCM patients as compared with genotype-negative HCM and healthy controls.[15,16] Hinojar et al[17] took these findings one step further to examine whether it is possible to use CMR imaging to differentiate between patients with hypertensive heart disease with LVH (n=69), hypertrophic cardiomyopathy (n=95), and genotype-positive phenotype-negative (n=23) patients. In comparison to patients with LVH caused by hypertension, patients with HCM had longer native T1 times and increased extracellular volume, including in subsets with LV wall thickness >15 mm and those without LGE. Additionally, they found that genotype-positive phenotype-negative patients had increased native T1 times compared with healthy controls. The type of gene mutations for the genotype-positive phenotype-negative group was not detailed, nor are the details about genetic testing of the HCM group. The studies with available genetic testing results have not shown a difference in prevalence of LGE or native T1 times between patients with mutations in MYH7 or MYBPC3 genes.[16,18]

Current studies on a genotype–phenotype correlation have also been limited because imaging is often conducted at one point in time, with mean clinical follow-up for outcomes ranging from 4 to 10 years. It is likely that the complete penetrance may appear later in the disease than when the patient is imaged.[9] Small longitudinal studies have suggested that there is progression of LGE in patients with HCM,[19] and thus imaging at a cross-section in time may not provide complete information on a phenotype associated with a particular gene mutation. Although it may be more feasible to conduct cross-sectional studies, especially with CMR imaging, the information gleaned may not be complete with regard to identifying phenotypes and risk for more severe outcomes such as sudden death or end-stage heart failure, especially with limited follow-up.

Human genetics can be used in medicine for a variety of different purposes: to identify those at risk to develop a disease, to offer insight into prognosis, or to target therapy. Current recommendations in HCM include the use of genetic testing to identify at-risk family members of patients with HCM for appropriate screening and, in uncertain cases, to discern from phenocopies like Fabry disease.[20] Although much headway has been made in exploring the underlying genetics of HCM, much remains to be explored regarding pathogenesis, epigenetics, and environmental factors influencing phenotypic penetrance for patients before we will be able to use genetic testing to predict prognosis and affect treatment modalities. This study adds further evidence that our current understanding of genetics is insufficient to predict clinical phenotype or outcomes. This complex issue is under continued study by ongoing clinical trials, one of which, HCMR trial (hypertrophic cardiomyopathy registry), seeks to collect clinical, genetic, echocardiographic, and CMR imaging data in ≈2700 patients with clinically diagnosed HCM.[21] This will

prove to be the largest, international cohort of patients examined yet to integrate clinical, genetic, and imaging data to further investigate the link between genotype and phenotype, with the added distinction that no >5 members of one family may be included, thus helping to eliminate some of the biases and provide more generalizable information. With regard to genetics in HCM, our task remains to improve the genetic signal-to-noise ratio to determine what additional information may be useful and integrated into patient care with regard to predicting phenotype and clinical outcomes.

Sources of Funding

The corresponding author acknowledges that he is supported by the Haslam Family Endowed Chair in Cardiovascular Medicine.

Disclosures

Dr Desai is a consultant for Myokardia, Inc. Dr Desai is on the steering committee of the HCMR (hypertrophic cardiomyopathy registry) trial sponsored by the the National Institutes of Health. The other author reports no conflicts.

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KEY WORDS: Editorials ■ cardiomyopathy, hypertrophic ■ fibrosis ■ genetics ■ human ■ magnetic resonance imaging

Circulation
Cardiovascular Imaging

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Circ Cardiovasc Imaging. 2017;10:
doi: 10.1161/CIRCIMAGING.117.006066
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080