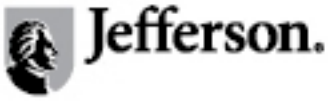

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Research priorities in hypertrophic cardiomyopathy: report of a Working Group of the National Heart, Lung, and Blood Institute.

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Special Report

Research Priorities in Hypertrophic Cardiomyopathy

Report of a Working Group of the National Heart, Lung, and Blood Institute

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Hypertrophic cardiomyopathy (HCM) is a myocardial disorder characterized by left ventricular (LV) hypertrophy without dilatation and without apparent cause (ie, it occurs in the absence of severe hypertension, aortic stenosis, or other cardiac or systemic diseases that might cause LV hypertrophy). Numerous excellent reviews and consensus documents provide a wealth of additional background.[1–8] HCM is the leading cause of sudden death in young people and leads to significant disability in survivors. It is caused by mutations in genes that encode components of the sarcomere. Cardiomyocyte and cardiac hypertrophy, myocyte disarray, interstitial and replacement fibrosis, and dysplastic intramyocardial arterioles characterize the pathology of HCM. Clinical manifestations include impaired diastolic function, heart failure, tachyarrhythmia (both atrial and ventricular), and sudden death. At present, there is a lack of understanding of how the mutations in genes encoding sarcomere proteins lead to the phenotypes described above. Current therapeutic approaches have focused on the prevention of sudden death, with implantable cardioverter defibrillator placement in high-risk patients. But medical therapies have largely focused on alleviating symptoms of the disease, not on altering its natural history. The present Working Group of the National Heart, Lung, and Blood Institute brought together clinical, translational, and basic scientists with the overarching goal of identifying novel strategies to prevent the phenotypic expression of disease. Herein, we identify research initiatives that we hope will lead to novel therapeutic approaches for patients with HCM.

Epidemiology

The epidemiology of HCM suggests that it is present in ≈1 in 500 adults.[9] Because of the delay in phenotypic expression of the disease, HCM is not commonly recognized clinically in young children, but when it is, it is much more frequently recognized in males.[10] This is likely due to greater penetrance in young males.[11,12] HCM is underdiagnosed clinically in blacks and in women, yet women tend to present with more marked heart failure than men when they are diagnosed later in life.[13,14] There is no overall difference in mortality, including sudden cardiac death, between men and women, although sudden cardiac death on the athletic field predominantly occurs in men.

Genetic Cause

Extensive investigation has shown that at least 50% of HCM cases can be traced to a specific genetic cause. This probably underestimates the true percentage of genetically based HCM, because current mutation-screening platforms typically examine only 8 to 10 genes because of unfavorable cost-benefit assessments. For example, current platforms do not examine titin (owing to its size) or myozenin-2 (because relatively few mutations have been defined in this gene).[15]

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Moreover, when strict clinical criteria are used for diagnosis, including family history, mutation detection approaches 70%.

HCM is a genetic disease of sarcomere proteins,[5,16] with mutations in the genes that encode β-myosin heavy chain (*MYH7*) and myosin binding protein C (*MYBPC3*) accounting for ≈80% to 85% of cases with identified mutations in most series.[4,17–19] Mutations in the troponins cardiac troponin T (*TNNT2*) and troponin I (*TNNI3*) and α-tropomyosin (*TPM1*) are also relatively common, collectively representing 10% to 15% of additional genetic causes for all HCM cases.[4,17,19] These and the myosin light chains (*MYL2*, *MYL3*) and α-cardiac actin (*ACTC*) are the 8 genes most commonly involved in HCM.

Rare Genetic Causes

Mutations in several other genes that encode sarcomere or sarcomere-related proteins have been implicated in HCM, including cardiac troponin C (*TNNC1*), α-myosin heavy chain (*MYH6*), and cardiac myosin light chain kinase 2 (*MYLK2*). In addition, several other genes that encode non-sarcomere proteins, including caveolin 3 (*CAV3*), calreticulin (*CALR3*), junctophilin-2 (*JPH2*), phospholamban (*PLN*), and the mitochondrial tRNA-encoding genes *MTTG* and *MTTI*, produce clinical features that mimic HCM.[4,20] The relationship of HCM caused by sarcomere protein gene mutations to these disorders is unclear.[5,16]

Unknown Causes

The apparent absence of mutations in patients with a clinical diagnosis of HCM indicates an important gap in our knowledge. Mutation testing can be particularly uninformative in 3 clinical scenarios in which family history is negative: (1) Hypertrophy that occurs very early in childhood; (2) hypertrophy that is only recognized after middle age; and (3) hypertrophy that is limited to the ventricular apex.[21] The cause of these conditions is not clear.

Disease Mechanisms

The disease mechanisms of HCM remain incompletely understood. Postulated mechanisms include (1) a dominant negative function (ie, a "poison peptide," wherein the mutant gene encodes a protein that interferes with the function of the normal allele); (2) haploinsufficiency (leading to an insufficient quantity of the normally functioning sarcomere protein); and/or (3) impaired myocardial energetics and decreased energy reserve.[8,22,23] The lack of a definitive link between mutations and an understanding of the pathogenesis/molecular mechanisms that drive the expression of the HCM phenotype is a significant gap in our understanding of the disease.

Clinical Genetics

Allelic heterogeneity (each family having a so-called private mutation) is particularly common in HCM. Approximately 500 mutations have been noted in the medical literature, but the number of identified mutations in various private databases suggests the true number is more than 1000. HCM demonstrates age-dependent penetrance, affecting 50% to 80% and 95% of individuals by age 30 years and ages 50 to 60 years, respectively.[24] Recent estimates of 1% annual mortality in HCM differ significantly from earlier estimates (3% to 6%) that were based on referral populations of high-risk groups to HCM centers.[25–27] Survival to 75 years or beyond has been estimated in ≈25% of an unselected HCM cohort.[28]

Compound Heterozygosity

Two to five percent of patients with HCM harbor 2 mutations (compound or double heterozygosity) or are homozygous for a mutation,[4,18,29,30] and these patients display more severe and/or earlier onset of disease.[29,30]

Genotype/Phenotype Relationships

Despite the significant clinical heterogeneity observed even for the same mutation within families or between families,[31–35] as well as the variable penetrance, which alters clinical onset and severity of disease, genotype/phenotype relationships of sarcomere gene mutations clearly have advanced our understanding of the disease and, in some cases, have allowed identification of relatively low- versus high-risk patients.[36,37] Some genotype/phenotype relationships that have stood the test of time include *MYH7* mutations, which are associated with earlier onset and more extensive hypertrophy.[8,33,35] More specifically, the myosin 403 mutation is associated with increased risk of heart failure and sudden death, and the myosin 719 mutation leads to a marked increase in heart failure. Others include the relatively limited hypertrophic response with *TNNT2* mutations[34,38,39] and the incomplete penetrance and relatively later onset of HCM from *MYBPC3* mutations.[31,36,40] That said, multiple poorly understood mechanisms contribute to heterogeneity of presentation, and these include environmental inputs, sex,[10] and genetic and epigenetic modifiers.

Key Morphological and Clinical Components of Genetically Mediated HCM

Cardiomyocyte and cardiac hypertrophy, myocyte disarray, interstitial and replacement fibrosis, and dysplastic intramyocardial arterioles characterize the pathology of HCM. Clinical manifestations include impaired diastolic function, tachyarrhythmia (both atrial and ventricular), and sudden death.[41–44] Accepted risk factors for sudden cardiac death include prior cardiac arrest from ventricular fibrillation, spontaneous sustained ventricular tachycardia, family history of premature sudden death, unexplained syncope, LV wall thickness ≥30 mm, abnormal blood pressure response to exercise, and nonsustained ventricular tachycardia.[28,43] Additional predictors include the presence of LV apical aneurysms and the end stage of disease.[45,46]

A consensus document[1] and review[47] of clinical management of arrhythmias and sudden cardiac death in HCM are available. Clinically apparent atrial fibrillation develops in at least 20% of patients with HCM,[48] but the true incidence is likely higher than that. Atrial fibrillation is a risk factor for thromboembolic disease, including stroke.[1] Molecular mechanisms that regulate the phenotypic expression of the various pathologies and how these might drive arrhythmogenesis in HCM are poorly understood.

Genetic Causes of LV Hypertrophy Not Involving Sarcomere Mutations

LV hypertrophy can result from gene mutations that alter proteins with functions that are unrelated to the sarcomere. These

include Fabry disease, glycogen storage disorders (PRKAG2 cardiomyopathy and Pompe disease), lysosomal disorders (X-linked lysosome-associated membrane protein gene cardiomyopathy), and several syndromes (ie, Noonan, lentigines, ECG abnormalities, ocular hypertelorism, pulmonary valve stenosis, abnormal genitalia, retardation of growth, and deafness [LEOPARD], and Costello). The clinical manifestations and patient courses associated with these are different from HCM.[8,17,49–51] These phenocopies are not discussed further herein.

Rationale for Investing in Research on HCM

The rationale for investing in research in HCM is supported by the following: (1) HCM is the most common genetic heart disease and affects individuals at every age; (2) HCM is the most common cause of sudden death in young people; (3) HCM is an important cause of heart failure disability; (4) HCM can be viewed as a paradigm for the potential opportunities provided by harnessing modern genetic science in medicine to make gene-based diagnosis and prediction a reality; (5) gaps in our basic understanding of mechanisms of disease are substantial, but already, insights provided by studies in patients and in animal models of HCM suggest creative strategies to alter the natural history of this disease; and (6) these insights also promise a greater understanding of the molecular pathophysiology of other, nongenetic causes of hypertrophy. Thus, we believe that there are unparalleled opportunities in the immediate and near future to translate basic insights about HCM into new clinical models for diagnosis, prevention, and therapy.

Critical Deficits in Our Understanding of HCM Pathogenesis Define Research Initiatives

In the online-only Data Supplement to this report, we define key deficits in our understanding of HCM, thereby leading into a delineation of research initiatives for the future. The areas of research will be broken down into clinical, translational, and basic science sections, but these divisions are clearly arbitrary and only serve as an organizational (and not operational) tool. In fact, we will strive to maintain connections among the 3 divisions, focusing on common deficits in our understanding.

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