MOLECULAR GENETICS OF HYPERTROPHIC CARDIOMYOPATHY

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a primary disease of the myocardium characterized by unexplained cardiac hypertrophy, a small left ventricle and increased left ventricular ejection fraction. HCM is the most common cause of sudden cardiac death (SCD) and a major cause of morbidity in the elderly. The prevalence of HCM is approximately 1:500 in the young, general population and likely higher in older individuals because of age-dependent penetrance.1 There have been remarkable advances in molecular genetic studies of HCM that have potential implications in understanding the pathogenesis, early diagnosis, risk stratifications and development of new therapies.

PHENOTYPIC EXPRESSION OF HCM

The maiority of patients are asymptomatic. In those symptomatic, the most common symptoms are dyspnea, chest pain, palpitations, dizziness, lightheadedness and sometimes syncope, a serious manifestation often associated with cardiac arrhythmias and increased risk of SCD. Cardiac arrhythmias are relatively common, with atrial fibrillation and non-sustained ventricular tachycardia being the most predominant. SCD is uncommon bur tragic since it can be first manifestated in young, apparently healthy individuals.2,3 Phenotypes associated with the risk of SCD are listed in Table 1. Nonetheless, HCM is considered a relatively benign disease with an annual mortality of about I% in adults.4,5

Cardiac hypertrophy is asymmetric in two-thirds of HCM cases, with predominant involvement of the inter-ventricular septum. Hypertrophy may be localized to the heart's apex, the lateral wall and, rarely, the posterior wall. Left ventricular chamber size is small, and although the ejection fraction is preserved or increased, myocardial contraction and relaxation are impaired.6 Diastolic dysfunction is the primary cause of heart failure symptoms in patients with HCM.

Cardiac myocyte disarray is the pathological hallmark of HCM, often comprising more than 20% of the ventricle (normal < 5%).7,8 Myocyte disarray is more prominent in the inter-ventricular septum but also present throughout the myocardium.8 Myocyte hypertrophy and interstitial fibrosis while common, are not diagnostic pathological features. Cardiac hypertrophy, interstitial fibrosis, and myocyte disarray are associated with the risk of SCD, mortality and morbidity in patients with HCM.9-12

MOLECULAR GENETIC BASIS OF HCM

HCM is a genetic disease with an autosomal dominant mode of inheritance in approximately half of the patients. It is a sporadic disease in the remainder. The molecular genetic basis of HCM is all but elucidated, with more than a dozen genes and 200 mutations identified (Table 2)_13,14 HCM is considered a disease of mutant contractile sarcomeric proteins.15 It is noteworthy, however, that a similar phenotype could also occur in storage disease and is not considered true HCM since it lacks true myocyte hypertrophy or disarray. Genetic screening studies suggest that approximately 80% of the causal genes and mutations have already been identified.14, 16 The HCM causal genes encoding b-MyHC (MYH7), myosin binding protein-C (MYBPC3), cardiac troponin T (TNNT2) and cardiac troponin I (TNN13) collectively account for approximately 70% of all HCM cases.14,17

Genetic factors other than the causal genes also affect phenotypic expression of HCM and are referred to as "modifier genes." Modifier genes are neither necessary nor sufficient to cause HCM, but do affect the severity of the phenotype.

Table 1.

RISK FACTORS FOR S.C.D. IN PATIENTS WITH H.C.M.

- Previous history of aborted SCD
- Family history of SCD (more than one SCD victim in the family)
- History of syncope
- Certain causal mutations and modifier genes
- Severe hypertrophy
- Severe outflow tract obstruction
- Severe interstitial fibrosis and myocyte disarray
- Early onset of clinical manifestations (young age)
- Sustained and repetitive non-sustained ventricular tachycardia
- Abnormal blood pressure response to exercise
- Presence of myocardial ischemia (in children)

GENE	LOCUS	FREQUENCY
-Myosin heavy chain	14q12	~3%
Myosin binding protein-C	11p11.2	~3%
Cardiac troponin T	1q32	~5-1%
Cardiac troponin I	19p13.2	~5-1%
a-tropomyosin	15q22.1	<5%
Myosin light chain-1	3p21.3-p21.2	<5%
Myosin light chain-2	12q23.q24.3	<5%
Cardiac a-actin	11q	<5%
Titin	2q24.1	<5%
a-Myosin heavy chain	14q	Rare
Tcap (Telethonin)	10q12	Rare

Table 2. Causal Genes for HCM

These effects were first demonstrated for the angiotensin-1 converting enzyme 1' (ACE-1) gene variants, which were linked to severity of cardiac hypertrophy and risk of SCD.18-lO The vast majority of the modifier genes have not yet been identified.

Genotype-Phenotype Correlation: The results of genotype-phenotype correlation studies suggest that mutations affect the severity of cardiac hypertrophy and the risk of SCD.[21-28] Overall, the -MyHC mutations are associated with an early onset, extensive hypertrophy and a relatively higher incidence of SCD, whereas mutations in the MyBP-C are associated with late onset and relatively mild hypertrophy.21,[2]9.30 The relatively low penetrance of certain mutations indicates that one can not exclude the possibility of HCM based on a normal physical examination, electrocardiogram and echocardiogram at a young age as the disease could develop at a later age. It is important to note that there is significant variability in the phenotypic expression of mutations, and benign and malignant mutations in each gene have been described. In general, mutations in cTnT and cTnl are usually associated with mild cardiac hypertrophy, a higher incidence of SCD and extensive myocyte disarray.12,[26]

Concomitant diseases that increase cardiac load, such as hypertension, can also accelerate phenotypic expression of HCM, including mutation penetrance and hypertrophic severity. This is best illustrated in hypertensive hypertrophic cardiomyopathy of the elderly, a form ofHCM caused by MyBP-C mutations and often manifesting from hypertension.29

PATHOGENESIS OF HCM

The link(s) between the causal genetic defect and HCM's various phenotypic expressions is not precisely known. Existing data suggests that the initial phenotypes are largely biochemical and functional, such as reduced myofibrillar ATPase activity and impaired interaction of the sarcomere componencs.31 Functional phenotypes lead to expression of intermediary molecular phenotype – e.g. activation of intracellular signaling molecules - which collectively mediate induction of structural and histological phenotypes such as hypertrophy, fibrosis and disarray, among others. According to this hypothesis, cardiac hypertrophy is considered a compensatory phenotype likely induced by myocardial contraction and bioenergetics.3!-35 For example, a recent study showed that tissue Doppler velocities of myocardial contraction and relaxation were reduced in patients with HCM mutations before they developed cardiac hypertrophy,6 and similar evidence has shown the myocardium's "energy compromise" based on reduced ratio of cardiac phosphocreatine to adenosine triphosphate.3[6]

Genetic Screening: In theory, genetic screening could potentially identify family members at risk of developing HCM prior to and independent of its clinical manifestations – ultimately leading to generic risk stratification and preventative genetic-based interventions. Yet despite our ability ro identify most HCM causal genes, the diversity and infrequency of these specific causal mutations has made it difficult m develop and implement routine genetic screening, and low pre-test probability rules out the possibility of screening for a selected number of mutations.

A desirable genetic screenmg approach requires high sens1t1v1ty and specificity of the screening technique at a reasonable cost. The current technique for mutation detection is direct sequencing of genomic DNA, which is both sensitive and specific. However, diversity of the causal genes requires sequencing of at least a dozen genes that collectively comprise more than 100,000 nucleotides - a technique that is costly and labor intensive and would have, at best, an 80% chance of identifying the causal mutation. A practical compromise is to limit

che sequencing to HCM's four most common causal genes, which could identify approximately two-thirds of the mutations. Hopefully within the next few years, advanced mutations screening techniques will be applied on a routine basis to screen at-risk individuals.

IMPACT OF GENETICS ON TREATMENT OF HCM

Medical treatment of HCM has remained unchanged during the past two decades and includes blockers, calcium channel blockers and, less commonly, disopyramide phosphate and amiodarone, the latter to treat arrhythmias. More importantly, current therapeutic interventions have not induced regression of cardiac hypertrophy, fibrosis or disarray. It is still not feasible to correct the underlying generic defect. Therefore, research has focused on blockading the intermediary molecular phenotypes, such as blocking signaling kinases that induce hypertrophy and fibrosis. Treatment with simvastatin was recently found to attenuate cardiac phenotypes and induce regression of hypertrophy and fibrosis in a transgenic rabbit model of human HCM.37 Several recent studies have corroborated the potential benefits of statins, yet it is unclear whether the findings could extend to humans.

Other notable animal-model studies include the use of spironolactone or losartan to reverse interstitial fibrosis, a risk factor for cardiac arrhythmias and SCD.9,38,39 The results raise the possibility of using renin-angiotensin-aldosterone-system inhibitors to treat patients.

CONCLUDING REMARKS

HCM is the most common cause of SCD in the young and a major cause of morbidity and mortality in the elderly. Its molecular genetic basis is largely known, and current research aims to develop genetic screening techniques to identify those at risk. Studies in transgenic animal models have shown potential utility of statins or renin-angiotensin-aldosterone-sysrem blockade in reversing and attenuating HCM cardiac phenotypes, but more studies are needed to determine whether these new pharmacological interventions also benefit humans.

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