HYPERTROPHIC CARDIOMYOPATHY: GENETICS

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Hypertrophic cardiomyopathy (HCM) is the most common of the genetic cardiovascular diseases, characterized by heterogeneity in its cause, phenotypic expression and management options. The prevalence of HCM in the general population is at least 0.2% (1:500), is transmitted as an autosomal dominant trait, affecting males and females equally. HCM occurs worldwide, has been reported from all continents and more than 60 countries. The disease is caused by mutations in a variety of genes encoding proteins of the cardiac sarcomere.

Clinical presentation/course

HCM is characterized by variable clinical presentation and natural history, ranging from preventable sudden death, from ventricular tachyarrhythmias, to progressive heart failure, to the consequences of embolic stroke. Patients with HCM may display a variety of symptoms. Exertional dyspnea, exercise intolerance and fatigue reflect heart failure and may be associated with chest pain (which can be typical angina pectoris, even in the absence of coronary artery disease). Such symptoms of exertional dyspnea are usually due to 3 possible mechanisms: (1) Left ventricular (LV) outflow obstruction which produces elevated LV intraventricular pressures and wall stress; (2) diastolic dysfunction and impaired LV filing from the noncompliant and thickened wall; and (3) myocardial ischemia from the small vessel disease. However, it should be emphasized that HCM is also frequently compatible with normal life expectancy, often without disability or the need for major interventions to achieve that outcome. The diagnosis of HCM is most commonly made following onset of symptoms.

Genetics of HCM

HCM is transmitted in an autosomal dominant pattern of inheritance. Therefore, an individual carrying a disease-causing HCM mutation has a 50% chance of transmitting the mutation to a child, either male or female. Molecular genetic studies have defined HCM as a disease of the sarcomere, the contractile unit within the cardiac myocyte that is comprised of thick and thin filaments.

HCM has proved to be a genetically heterogeneous condition and to date 18 disease-causing genes and >500 individual mutations have been identified (Figure 2 and Table 1). Mutations in these genes have been identified in 40-60% of HCM cases (the majority of which are missense mutations with amino acid substitution). Many of these mutations have proved to be unique to individual families. Mutations in ß-

myosin heavy chain (MYH7) and myosin-building protein C (MYBPC 3) account for the majority of identified mutations.

Genes involved in HCMGene	Name
ACTC	Alpha Cardiac actin 1
CAV3	Caveolin 3 (Muscular dystrophy)
GLA	Galactosidase alpha (Fabry)
LAMP2	Lysosome-associated membrane protein 2
MTTG	Mitochondrial transfer RNA glycine
MTTI	Mitochondrial transfer RNA isoleucine
MTTK	Mitochondrial transfer RNA lysine
MTTQ	Mitochondrial transfer RNA glutamine
MYBPC3	Cardiac myosin-binding protein C
MYH7	ß – Myosin heavy chain
MYL2	Regulatory myosin light chain 2
MYL3	Essential myosin light chain 3
PRKAG2	Noncatalytic AMP-activated protein kinase gamma 2
TNNC1	Troponin C
TNNI3	Cardiac troponin I
TNNT2	Cardiac troponin T
TPM1	Tropomyosin 1
TTR	Transthyretin (Amyloidosis)

Genetic testing for Hypertrophic Cardiomyopathy (HCM) and its utility:

Diagnostic genetic testing can be considered for patients who clinically manifest with symptoms of HCM and for patients who are asymptomatic but are within a family with a known mutation. Testing should be performed first on the family member who is symptomatic, i.e. has clinical manifestations of HCM. Preferably, the youngest of most severely affected family member should be tested first. The three possible outcomes of genetic testing are: positive, negative, and variant of unknown clinical significance (VOUS). Identification of a mutation in the family can lead to genetic identification of at risk family members who are clinically asymptomatic and who may have normal echocardiograms. Family members who test positive for the familial mutation should receive regular echocardiographic surveillance. Alternatively, a negative genetic test result for the familial mutation would obviate the need for repeated follow-up examinations. Genetic testing may be useful when discerning “athlete’s heart” from HCM. Genetic testing can be used for prenatal diagnosis. All patients who undergo genetic testing should receive pre-test and post-test genetic counseling to understand the implications of testing.