Summary

In recent years, molecular genetic studies in humans have shown that abnormal cardiac growth can result from molecular alterations within the myocardium, unrelated to changes in afterload. In humans, mutations in genes encoding components of the contractile apparatus of the cardiac myocyte produce familial hypertrophic cardiomyopathy (FHC). FHC is genetically heterogeneous and all the known disease genes encode sarcomeric proteins: β-myosin heavy chain, cardiac troponin T, α-tropomyosin, cardiac myosin binding protein C, essential and regulatory myosin light chains and cardiac troponin I. There is also a striking allelic heterogeneity, and more than 100 mutations were found so far. The two major genes are those encoding β-myosin heavy chain (MYH7) and cardiac myosin binding protein C (MYBPC3). The clinical relevance of these observations will be discussed.

Introduction

In recent years, molecular genetic studies in humans as well as the capacity to selectively mutate genes or create excessive or deleted gene expression in muscle have shown that abnormal cardiac growth can result from molecular alterations within the myocardium, unrelated to changes in afterload. In humans, mutations in genes encoding components of the contractile apparatus of the cardiac myocyte produce hypertrophic cardiomyopathy. It is a complex cardiac disease with unique pathophysiological characteristics and a great diversity of morphologic, functional and clinical features.1,2 Although hypertrophic cardiomyopathy has been regarded largely as a relatively uncommon cardiac disease, the prevalence of echocardiographically defined hypertrophic cardiomyopathy in a large cohort

of apparently healthy young adults selected from a community-based general population was reported three years ago to be as high as 0.2%. Familial disease with autosomal dominant inheritance predominates and is usually referred to as familial hypertrophic cardiomyopathy (FHC).

FHC is characterized by left and/or right ventricular hypertrophy, which is usually asymmetric and which can affect different regions of the ventricle. The interventricular septum is most commonly affected, with or without involvement of either the anterior wall or the posterior wall in continuity. A particular form of regional involvement affects the apex but spares the upper portion of the septum (apical hypertrophy). Typically, the left ventricular volume is normal or reduced. Systolic gradients are common. Typical morphological changes include myocyte hypertrophy and disarray surrounding the areas of increased loose connective tissue. Patients with hypertrophic cardiomyopathy frequently report a reduced exercise capacity and functional limitation. Although the pathophysiological features of the disease that contribute to this limitation are complex and not fully understood, left ventricular outflow tract obstruction if present, is believed to contribute to increased filling pressures and a failure to augment cardiac output during exercise, leading to exertional symptoms. Arrhythmias and premature sudden deaths are common.

Disease genes for FHC

The first gene for FHC was mapped to chromosome 14q11.2-q12 using genome-wide linkage analysis in a large Canadian family. Soon afterwards, FHC locus heterogeneity was subsequently reported and confirmed by the mapping of the second FHC locus to chromosome 1q3 and of the third locus to chromosome 15q2. Carrier et al. mapped the fourth FHC locus to chromosome 11p11.2. Four other loci were subsequently reported, located on chromosomes 7q3, 3p21.2-3p21.3, 12q23-q24.3 and 19p13.2-q13.2. Several other families are not linked to any known FHC loci, indicating the existence of additional LQTS-causing genes.

All the disease genes encode proteins that are part of the sarcomere which is a complex structure with an exact stoichiometry and multiple sites of protein-protein interactions (Table 1, Figure 1 and review in): three myofilament proteins, the β-myosin heavy chain