Hypertrophic cardiomyopathy and contractile proteins

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Hypertrophic cardiomyopathy (HCM) is an inherited cardiomyopathy characterised by myocardial hypertrophy, usually of the left ventricle, in the absence of other loading conditions such as hypertension. HCM affects 1 in 500 of the general population, and is an important cause of sudden cardiac death in the young, particularly in athletes. HCM shows extreme clinical heterogeneity, with many individuals experiencing minimal or no symptoms, while others may suffer the most severe outcomes of heart failure and sudden death.

HCM is inherited in an autosomal dominant manner. Mutations in at least 13 sarcomere, or sarcomere-related genes have been identified to cause HCM (Maron *et al.*, 2012). While much is known about the genetic causes of HCM as well as the major clinical outcomes, relatively less is known about the mechanisms that underpin the development of HCM. A number of mechanisms have been implicated which encompass abnormalities in energy production, dysregulated calcium signaling, and changes in extracellular matrix production with the development of myocardial fibrosis (Tsoutsman *et al.*, 2013). Classical molecular signatures of mRNA and microRNA expression have been implicated in mouse models of HCM (Bagnall *et al.*, 2012). Furthermore, a “gene dose” effect may also be important. Recent studies have suggested patients with HCM who carry two or more pathogenic mutations have an earlier age of presentation, more severe left ventricular hypertrophy, and an increase in sudden death events (Ingles *et al.*, 2005). This severity of multiple mutation HCM has also been replicated in relevant mouse models (Tsoutsman *et al.*, 2008).

Understanding how mutations in contractile proteins lead to HCM will be critical as we aim to develop better diagnostic approaches, as well as identify new possible molecular targets for disease treatment and prevention. It is likely that a combination of human studies, relevant animal models, and cell culture systems will provide a platform for further discoveries relating to contractile proteins and HCM.

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