Editorial

Familial hypertrophic cardiomyopathy: man, mouse and cat

Since the identification of the first disease-associated mutation in β-myosin heavy chain in 1990, there has been an explosion of genetic information on familial hypertrophic cardiomyopathy (HCM). 1 Eight years later, despite tremendous progress, including the incrimination of seven different genes and over 100 attendant mutations, we find ourselves in a rather difficult position. Despite our sophisticated genetic diagnostic skills, we lack the concomitant therapeutic advances. 2 The study of HCM in animal models may help us out of this awkward situation.

Insights from molecular genetic investigations have helped clarify some of the clinical issues surrounding HCM in man, but these relate mainly to diagnosis and prognosis. While it has been known for some time that HCM is an autosomal dominant condition, the conventional view (based on clinical studies) is that the disease is only familial in 50% of cases. Recent molecular genetic work reveals that familial disease accounts for greater than 90% of hypertrophic cardiomyopathy, with the important implication that clinical screening should always be considered in all in first-degree relatives (i.e. parents and siblings as well as children). 3 The discrepancy between clinical and genetic diagnosis reflects the fact that HCM is a challenging disease to diagnose, such that affected relatives may be missed by clinical screening. In part this is because of its delayed phenotypic expression, classically thought to manifest in early adulthood, but now documented to occur much later in older patients with mutations in cardiac myosin-binding protein C (MyBP C). 3 In addition, these recent studies have also confirmed the existence of carriers (i.e. individuals who have no demonstrable abnormality on ECG or echocardiogram but are found to have an inherited mutation) and, more commonly, individuals with subtle abnormalities not sufficient to fulfill standard diagnostic criteria but who are nevertheless affected. In both categories, offspring are at the same risk of inheriting disease as those of overtly affected individuals.

The complex genetic heterogeneity of HCM, which makes molecular genetic diagnosis still a research laboratory task, does lend itself to a clinically useful genetic classification. Certain disease genes are associated with a particular natural history of the disease, and individual mutations appear to influence the prognosis quite markedly. 3–5 Because the extent of hypertrophy does not correlate with the risk of sudden death, such prognostic information can be informative over and above the clinical evaluation of patients.

Genotypic heterogeneity is also one of the challenges of understanding the mechanisms contributing to HCM. The current unifying hypothesis is that HCM is a disease of the sarcomere, since disease-causing mutations have now been found in seven different genes which encode sarcomere proteins. Mutations in β-myosin heavy chain (MHC), cardiac troponin T (cTnT) and MyBP C are thought to be the most common causes of HCM, but mutations have also been found in cardiac troponin-I, α-tropomyosin, and myosin essential and regulatory light chains. Most of the mutations are point mutations resulting in a change in a single amino acid. Growing evidence indicates that these encode mutant proteins that act as ‘poison polypeptides’ that interfere with sarcomere function; as such these can be modelled by expression in vitro for biochemical and biophysical analyses. 6 At least for MHC and TnT, mutant peptides appear to cause a primary hypocontractile response—indicating that the pathognomonic hypertrophy of HCM is a compensatory response. But other mutations (insertions, deletions, and splice site changes) are predicted to result in truncations of the encoded protein which might fail to incorporate into the sarcomere. Here, in particular, investigations of the underlying cellular mechanisms in HCM have been hindered by lack of availability of myocardium from affected individuals. In many cases the predicted truncations have not been confirmed by protein analysis due to lack of available tissue. In addition to providing confirmation of the predicted effect of the coding mutations, access to affected tissue samples would allow for functional assays to advance understanding of the underlying defects caused by a given mutation. Functional assays have been undertaken using various in vitro systems, e.g.
quail myotubes or bacterial expression systems, but there is ample evidence to suggest that the specific ambiance created by various modifying factors is important to the expression of the disease in a given individual.

Important questions remain regarding the way in which the causal mutations translate into clinical disease; answers to these may hold the key to potential interventions. Individuals with an HCM-causing mutation only manifest the disease in adult life, and only in certain regions of the heart. Within families, there is substantial phenotypic heterogeneity among individuals sharing the same mutation, with some individuals not manifesting the disease at all. Hence, protective mechanisms must exist which sometimes allow the heart to compensate for the underlying contractile deficit. Some of these factors are likely to be genetic. First, the mutation itself may influence the morphology of the disease. For example, individuals with cTnT mutations tend to manifest little hypertrophy and yet as a group are more likely to suffer sudden death than individuals with β-MHC mutations and substantial hypertrophy. Work by Epstein et al. suggests that a certain pattern of hypertrophy causing midcavity obstruction is most commonly observed in individuals with mutations in the myosin light chain genes. However, Kimura et al. showed that distinctly different patterns of hypertrophy, e.g. apical versus global, may be identified within the same family affected by the same mutation. Second, the genetic background of an individual may underlie the intrafamilial variation. Such modifier genes would be important candidates for genetic predisposition to acquired forms of cardiac hypertrophy, and hence very important risk factors in their own right. Unfortunately, it is uncertain whether genetic mapping in human HCM families will be of sufficient power to locate such modifier loci.

Therapeutic progress has also been hindered by several of the characteristics of HCM, and this relates both to evaluation of existing therapeutic options and derivation of novel therapies based on the underlying biology. It is not surprising that the existing literature and clinical experience is conflicting, as trials of drugs or other interventions have likely been performed in genetically disparate groups of patients with very different prior odds of an adverse outcome. Additionally, the substantial phenotypic heterogeneity makes patient comparison and clinical endpoints difficult to define. Delayed phenotypic expression complicates patient characterization and has limited studies to individuals with established hypertrophy. While it is now apparent that a large percentage of individuals with HCM may be asymptomatic at the time of diagnosis, we have yet to adequately evaluate the potential benefits and ethical issues of any pre-symptomatic therapies. Finally, the natural history of HCM would warrant relatively long-term, and therefore expensive, clinical trials. While studies in a genetically selected high-risk patient group would improve this situation, the numbers of genotyped patients will remain modest until molecular diagnostic technologies improve substantially. It is against this background that research efforts are focusing on the search for an appropriate animal model for HCM.

Transgenic mouse models have been generated for β-MHC and cTnT mutations, but while intriguing and useful information has been gleaned from these, they also reflect the potential limitations of this approach. Mouse models are likely to be useful in the functional analyses of the impact of the mutations on the contractile machinery. They will provide tissue to study the effects at the protein and cellular levels and, if engineered appropriately, should faithfully mimic the basic molecular pathology. Potentially, the mouse models will be invaluable for studying and manipulating the genetics of this disease, for example in targeting potential mediators of the hypertrophy response, and for the important search for modifying genes. On the other hand, the differences in size and heart rate are accompanied by major differences in contractile protein isoform expression and in the repertoire of adaptive responses. Thus far at least, the gross morphological phenotypes in the mouse do not faithfully mimic the human disease, indeed a transgenic mouse expressing a TnT mutation has a decreased heart size. There are theoretical problems with the design of the existing models which may underlie their disappointing phenotypes, but unless subsequent models faithfully recapitulate the compensatory hypertrophy and sudden death seen in man, therapeutic trials using genetically manipulated mice will be of questionable value in HCM.

HCM is the most commonly recognized feline heart disease, and the diagnosis of HCM is routinely made by echocardiography in domestic cats in veterinary practice. The characteristic morphologic features of HCM are precisely matched in cats and humans. Importantly, the natural history is also similar, as affected cats suffer arrhythmias, thromboembolic episodes, cardiac failure and sudden death. Thus the similarities with human HCM are sufficient to suggest that cats with HCM may represent a natural model for the human disorder and its clinical sequelae. Current work seeks to test the hypothesis that HCM results from contractile protein gene mutations in both species. At present, the obvious limitations of the cat model are the lack of genetic information and limited genomic resources. The literature describing HCM in the cat has not identified it to be a familial disease, and a genetic component has only been recently recognized in published abstracts. However, we have now documented numerous instances of an
affected cat with affected first-degree relatives, and we are studying a colony of Persian cats with an apparently autosomal dominant pattern of inheritance of HCM (unpublished data).

If HCM in the cat is found to share the molecular pathogenesis of HCM in man, then this finding would provide a convincing justification to pool investigational findings in both species. Trials of potential treatments in an affected cat populations could serve as a preliminary to trials in man, and might ultimately include treatment of pre-symptomatic mutation carriers. Such studies would initially test existing pharmacological treatments, but might in the future evaluate novel therapies developed as a result of a new biological understanding of the disease process. In this way, both veterinary and medical practice might finally benefit from therapeutic advances arising from the undoubted molecular genetic advances.

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References


