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Image Guided Cardiovascular Functional Genomics: Finding the Needle in the Haystack

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The vast amount of data generated by the human genome project has resulted in burgeoning genomic and pharmacogenomic associations but has increased the difficulty in identifying the genetic variant responsible for the clinical association. For example, information gained from the HapMap project facilitates efficient and cost effective genotyping of a gene using a "tagSNP" approach where one does not need to genotype all existing single nucleotide polymorphisms (SNPs) because genotypes at many polymorphic sites are strongly linked and therefore form linkage disequilibrium (or "LD") blocks. Consequently, one can genotype individual SNPs that "tag" or track with many others, providing maximum coverage per genotyping cost. However, the bulk sampling of the method makes it incapable of predicting which of the many linked SNPs has functional relevance. The field of functional genomics, or the use of bio-informatic, molecular, and physiologic tools to assess the functional relevance of candidate SNPs, is therefore emerging. Paralleling the emergence of functional genomics are dramatic advancements in non-invasive imaging reflected by continued improvements in current imaging approaches such as SPECT, PET, and MRI as well as the introduction of new technologies such as hybrid imaging that can be performed in both small animals and humans. Furthermore, there has been the rapid development of targeted as well as activatable contrast agents permitting imaging of biologically relevant processes with a high degree of sensitivity and specificity. As a consequence, non-invasive imaging is well-positioned to play a central role in identifying functionally relevant gene variants. The study by Tuunanen et al, published in this month's issue of the Journal represents an important first step in this regard. (1)

Hypertrophic cardiomyopathy (HCM) is a disease with a remarkable degree of phenotypic and genotypic heterogeneity, and the link between genotype and phenotype remains incompletely understood.(2) Several genetic factors may influence phenotypic variability among patients with HCM. To date 434 different "causal" mutations of sarcomeric protein genes have been identified, (http://genetics.med.harvard.edu/~seidman) and it appears that certain causal genes confer uncommon but characteristic clinical features.(3;4) Nevertheless, even within families where a single causal gene has been identified and shows the typical autosomal dominant transmission, affected family members may have variable degrees of phenotypic expression regarding their degree of left ventricular hypertrophy, sudden death and heart failure.(4) This has commonly been attributed to incomplete causal gene penetrance, where there is a lower than expected percentage of individuals with the genotype that exhibit the associated

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phenotype. There is also strong suspicion of a significant influence of as yet undefined modifier genes (genes other than the causal genes that are neither necessary nor sufficient to cause the disease but rather affect the severity of the disease phenotype) for individuals with HCM.(5) The interaction of the modifier gene or genes with the causal gene at any of many levels may exert an important influence on expression of a particular phenotype, but until such modifier genes are identified, this remains speculative. With these considerations in mind, a clear understanding of the determinants, genetic or otherwise, of fundamental physiologic processes of the myocardium in persons with HCM is lacking.

Most of the cardiac phenotypes (e.g. left ventricular hypertrophy, sudden death) studied in families with HCM are presumably late in the disease pathway. More sensitive imaging techniques may provide the capability to phenotype more subtle, “early” abnormalities. To shed light on the etiology of variability of myocardial metabolism and perfusion among patients with HCM, the study by Tuunanen et al in the current issue of JNC took a novel approach by using advanced imaging techniques in a group of patients with a single defined sarcomeric gene mutation but variable degrees of ventricular hypertrophy. In this paper, the authors use PET imaging to obtain exquisite phenotyping of individuals carrying a mutation for HCM. In this study, measurements of myocardial perfusion, oxidative metabolism and fatty acid metabolism are performed by PET in eight patients with HCM attributable to a known specific variant in the α-tropomyosin gene. The measurements were compared in these eight patients with 36 healthy volunteers. The authors observed that myocardial blood flow, oxidative metabolism and fatty acid uptake were inversely related to left ventricular mass. Furthermore when they subdivided the patient group into those with mild versus more moderate hypertrophy, they observed that those patients with mild hypertrophy exhibited higher levels of myocardial blood flow, oxidative metabolism, septal fatty acid uptake and left ventricular efficiency compared to those with more advanced hypertrophy. They also noted that in these patients in non-hypertrophied myocardial segments, myocardial oxidative metabolism and fatty acid uptake were significantly higher than compared with either hypertrophied segments or with normal controls. Similarly, myocardial blood flow was also significantly higher in non-hypertrophied segments in patients compared with normal controls. Based on this, these authors conclude that in this well defined patient population with HCM, increased myocardial perfusion and metabolism and efficiency characterize patients with mild hypertrophy whereas these hyper metabolic alterations decrease as hypertrophy becomes more advanced.

The results of the study highlight both the potential and the challenges of using advanced imaging techniques to help identify gene variants with clinically relevant phenotypes. For example, it is tantalizing to speculate that the relationship between the observed myocardial perfusion, metabolic, and efficiency patterns and the degree of left ventricular hypertrophy may represent differential penetrance of the gene variant or the effect of modifier gene(s), potentially helping in their identification. However, the small sample size and cross-sectional nature of the study design limits us to only speculating in this regard. Moreover, identifying abnormalities in perfusion and substrate metabolism may permit identifying relevant gene variants without waiting for more end-stage manifestations such as left ventricular remodeling and dysfunction to occur. Yet the complexity of the measurements will likely preclude their widespread use and, thus, demonstrate the need for imaging biomarkers that identify early phenotypes but are readily applicable. As these new approaches are developed and validated, finding the needle in the haystack will likely become easier.

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