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FOCUS ISSUE: BIOMARKERS

Where Genome Meets Phenome: Rationale for Integrating Genetic and Protein Biomarkers in the Diagnosis and Management of Dilated Cardiomyopathy and Heart Failure

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This review provides the rationale for integrating genomic and protein biomarkers in the evolving diagnosis and management of dilated cardiomyopathy (DCM) and its causal pathway to heart failure (HF), with a larger objective to serve as a template for genomic and phenomic profiling of other cardiovascular disease. DCM is a major cause of HF and accounts for more than half of heart transplantation in adults and children worldwide. DCM may remain asymptomatic for years, but HF and/or arrhythmias, both late manifestations of the disease, ultimately cause significant morbidity and mortality. A significant proportion of DCM has a genetic etiology. DCM can also result from environmental injury such as infection, toxins, or catecholamine excess. While molecular genetic testing can identify those at risk for genetic DCM, epigenetic and sentinel phenomic staging can help to identify those at highest risk in need for intervention. Phenomic staging includes integrating clinical and imaging features, transcriptomics, higher order proteomics and metabolomics interactions, and epidemiological data. This principle can be applied in family members of patients with DCM, where genetic testing and clinical phenotyping are indicated. This will allow the design of specific interventions tailored to individuals sharing similar risks, to alter the natural history of DCM and obviate complications such as HF/arrhythmias. (J Am Coll Cardiol 2012;60:283–9) © 2012 by the American College of Cardiology Foundation

Cardiovascular disease occurs as a cumulative consequence of the host's inadequate repertoire, often genetic, to respond to stress or injury. Symptoms typically occur late as a manifestation of failure of compensation. The intermediate stages of disease progression, including inflammation, growth, apoptosis, or autophagy, directly lead to tissue remodeling. This stage is often clinically silent, but offers the optimal opportunity for intervention. Common examples include the atherosclerotic plaque in coronary disease, asymptomatic left ventricular systolic dysfunction, or atrial remodeling prior to symptomatic fibrillation.

This review aims to apply current concepts of genomics and phenomics to the paradigm of dilated cardiomyopathy (DCM) and its progression to heart failure (HF). This includes genetic predisposition, imaging, and proteomics to characterize DCM in its preclinical stage, and targeted early intervention to prevent complications.

DCM, a disease of the myocardium, is defined by left ventricular enlargement and systolic dysfunction. In familial studies, DCM may be asymptomatic for years (1). Eventual symptoms include HF, arrhythmias or sudden death, or embolus from left ventricular thrombus. In contrast, HF is a symptom complex in which heart function is inadequate to meet physiological demands without presumption of etiology or systolic function.

Phenome, Genome, and Epigenome

Variation in the genetic repertoire (genome), together with the biological consequences and interactions with the environment, lead to molecular, biochemical, physiological, and clinical manifestations (phenome). We define the phenome here as the high-dimensional phenotype data for the entire organism (2), including not only clinical characteristics, but also information from cells, tissues, organs, and individuals (including epidemiological data), ranging from gene expression (transcriptomics), gene networks (integrative genomics [3]), and higher order proteomics and metabolomics interactions (2). The study of "genomics" in this context means

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Abbreviations and acronyms

BNP = brain natriuretic peptide

DCM = dilated cardiomyopathy

GWAS = genome-wide association studies

HF = heart failure

IDC = idiopathic dilated cardiomyopathy

MMP = matrix metalloproteinase

analyzing the genetic code for variants, both common and rare as well as single nucleotide changes or larger structural (copy number variant) changes, and understanding the total impact of gene variants on the phenome. Thus, the phenome integrates higher order interactions or systems biological networks (4) to better define transitional programs to disease.

Epigenetics defines the intersection of the genome, without changes to its nucleotide sequence, with the environment that leads to phenomic variations. Epigenetic mechanisms most commonly include methylation, acetylation, or nitrosylation patterns of modifications of gene function. Such epigenetic changes may be heritable, and the global changes are incorporated in the *epigenome*. An isogenic murine line with validated identical deoxyribonucleic acid (DNA) sequence can exhibit significantly different phenotypes due to differences in epigenetic modifications (Fig. 1) (5). Other examples include the paternally or maternally inherited predisposition to diabetes or post-natal cardiovascular risk from maternal intrauterine conditions (6).

DCM and Its Relationship to HF: Phenomics and Genomics Considerations

DCM, when applied without inference to any specific etiology, commonly presents with few phenotypic features that enable differentiating its etiology. Despite the well-established value (7) and now guideline-mandated use of family history as a means to detect genetically based DCM (8) because of familial clustering with Mendelian disease, family history alone is insensitive to detect familial DCM, even when ischemic and other detectable etiologies (aside from genetic) have been ruled out (commonly termed idiopathic dilated cardiomyopathy [IDC]). This is because asymptomatic systolic dysfunction, left ventricular enlargement, or DCM may be present for years with symptoms occurring only late in the causal pathway from (Fig. 2) (9). In addition, the age of onset of DCM varies widely, and ranged from 0 to 75 years in a familial DCM cohort from our group (10). Thus, even in family members genetically at risk to carry a DCM mutation, their DCM may not have yet presented and can only be identified with prospective clinical screening. Family history alone was found to detect 5% of familial disease (11), while clinical screening of relatives has been shown to detect familial DCM in 20% (11) to 48% of cases (see Burkett and Hershberger for review [1]). Combining family history with clinical screening of relatives, and emphasizing echocardiography to assess LV size and function, is essential to identify familial DCM (1,8).

DCM Genomics: Rare and Common Coding Variants

Most classical Mendelian disease is characterized by familial clustering of the phenotype of interest with a discernible pattern of inheritance, commonly resulting from very rare variants (e.g., ≤0.1% allele frequency) in coding sequence, thereby to change amino acids (termed nonsynonymous), invoke stop codons, alter splicing, or cause reading frames to shift (12). However, sequencing of genetic DCM has shown that the coexistence of multiple rare variants may also cause DCM (13,14).

Based on family studies, rare nonsynonymous mutations from >30 genes have been reported to cause nonsyndromic DCM (i.e., isolated DCM not associated with extra cardiac disease; lists of genes are available that cause syndromic DCM [9,15] or mixed phenotypes [e.g., arrhythmogenic right ventricular cardiomyopathy (16)]), even though they account for only ~45% to 50% of genetic DCM (12,15,17,18). The fractional contribution of each gene to DCM varies significantly: truncating variants in *TTN*, encoding titin, accounted for up to 25% of familial DCM (18), although most DCM genes have been shown to have much lower frequencies (e.g., *LMNA* 6%; *MYH7* 4%, *MYBPC3* 4%, *TNNT2* 3%, *MYH6* 3%, *SCN5A* 3%) (12). Most mutations are very rare or novel (19) and are usually specific to 1 individual or family (a "private" mutation). This makes both diagnostic and discovery approaches challenging, as it can be difficult to determine the true contribution of a newly identified variant to disease (12).

The gene ontology for DCM is shown (Table 1), with numerous genes encoding sarcomeric, z-disk, or cytoskeletal proteins. However, rare DCM mutations have also been

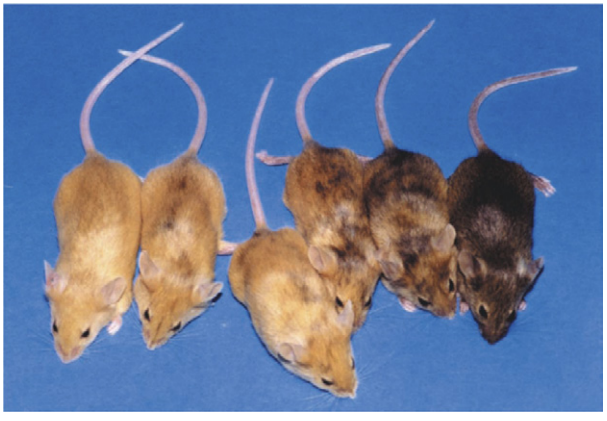

Figure 1 Epigenetic Regulation of Coat Color

These 6 mice have identical genomic DNA, as they are littermates from an isogenic line maintained by brother-sister matings for over 30 generations. The difference in coat color reflects variable expressivity of a cryptic promoter upstream from the coat color locus, a manifestation of a transcriptionally active retrotransposon that is epigenetically but variably reset during embryogenesis in each mouse. Adapted, with permission, from Whitelaw and Martin (5).