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Harnessing investigative genomics in heart failure

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Abbreviations: ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; AF, atrial fibrillation; CVDs, cardiovascular diseases; CHDs, congenital heart defects; DCM, dilated cardiomyopathy; 2DGE, 2-dimensional gel electrophoresis; FDA, food and drug administration; GWAS, genome wide association study; HCM, hypertrophic cardiomyopathy; HF, heart failure; HTN, hypertension; ICD, implantable cardioverter defibrillator; LCSD, left cardiac sympathetic denervation; LQTS, long qt syndrome; LVH, left ventricular hypertrophy; LVM, left ventricular mass; NGS, next generation sequencing; PTM, post translational modification; SCD, sudden cardiac death; SNPs, single nucleotide polymorphisms

Editorial

Before biotechnological tools were available sleuthing sudden cardiac death (SCD) was a major health problem and constituted an unsolved challenge due to our failure to determine its unexplained cause of death in teens and young adults. Now we know that most of those deaths were a result of heterogeneous genetic heart disorders, either structural cardiomyopathies or arrhythmogenic abnormalities leading to heart failure (HF). To some extent, developments in biology helped delineate functions of genetic elements however; the complexity could not be fully grasped. Systems biology is attempting to enable understanding the complex conditions such as HF since it can integrate observations stemming from genes and their respective products and thus could allow the study of cell's organization and its physiological behavior.[1] Concomitantly, a dramatic change in cardiovascular medicine has witnessed a sizable reduction in patients' morbidity and mortality. However, cardiovascular diseases (CVDs) still remain a serious concern globally and disappointingly its manifestation has considerably changed.[2] This shifting landscape presents many challenges and opportunities including application of investigative genomics along with the latest approaches such as next generation of sequencing (NGS).[3] These options could help develop newer generation of tests for diagnosis, prognosis and therapeutic interventions to monitor both acute coronary injuries and chronic heart diseases. The development of such tests should essentially take into account the role of genes or their encoded protein products not only to assess the risk of CVDs but also to treat patients accordingly.

During the last few years major progress has been made by encompassing genomic discoveries for designing and conducting clinical trials aiming to develop projects solely relying on human genomic information.[4] Thus, incoming future, 'omics' centered technologies based on one's genetic architecture are going to transform the way patients' screening, diagnosis, treatment and prevention of medically serious conditions are performed in well-equipped research and diagnostic centers around the world. However, the differences, limitations and benefits of these newer biomedical technologies, at present, remain unclear. This editorial brings an overview of the current challenges and future promises regarding life threatening medical conditions such as HF and the cutting-edge tools and related interventions that are going to make their way into our clinics, soon.

It all became possible largely due to human genome sequencing efforts that ushered an equal interest in researchers, clinicians and surgeons because the promise of genomics and genetics would allow for better choices concerning cardiac health management. Cardiomyopathies are primary disorders of cardiac muscle with abnormalities in wall thickness, chamber size, contraction, relaxation, conduction and rhythm. A large number of gene mutations have been found but their inheritance is modest and their implications, at present, are not well understood. For example, in hypertrophic cardiomyopathy (HCM), mutations at multiple chromosomal loci coding for contractile, cytoskeletal and Ca^{2+} regulatory elements have been shown. Similar genetic alterations can also lead to dilated cardiomyopathy (DCM) as well. Further, cardiomyopathies associated with arrhythmias have been linked with mutations in cardiac metabolic genes in association with ventricular pre-excitation and also with mutations causing arrhythmogenic right ventricular dysplasia in protein constituents of desmosomes. This heterogeneity suggests that there are multiple pathways that can lead to changes in heart structure and functions such as defects in myocytes' force generation, force transmission and Ca^{2+} homeostasis. Hence, delineation of the cellular and molecular events that are triggered by these mutations can provide new fundamental knowledge about myocytes' biology and organ physiology that accounts for remodeling and ultimately HF.[5]

Identification of important pathways became crucial since numerous molecules are involved in HF, including the β-adrenergic receptor, various kinases and the Ca^{2+} handling proteins. Mouse models presented alterations in expression of the genes or their receptors and products that did help uncover homeostatic mechanisms. As a result, a number of pathways were discovered that turned out to be the main regulators of myocardial functions.[6,7] In fact, unraveling the molecular complexities of HF, particularly end-stage failure, can be achieved by combining multiple approaches. There are several parts to the problem as each patient is a product of a complex set of genetic variations, different degrees of influence of diets and lifestyles and usually heart transplantation patients are treated with multiple drugs. Given the unknown long-term follow-up in many of these subjects, continued vigilance via genomic status of the myocardium of any one transplant patient can be analyzed using gene expression with its own strengths and weaknesses. The proteins expressed by these failing hearts were first investigated using two-dimensional gel electrophoresis (2DGE)

which promised to resolve several thousand proteins in a failing heart. However, 2DGE was successful for the abundant and moderately expressed proteins; it struggled to identify proteins expressed at low levels. Nonetheless, first dimension separations combined with advances in mass spectrometry can provide an alternative for solving this issue.[8]

In this era of genomics, new technologies and the information they generate have a wide range of potential applications in HF. Though there has not been wide spread use of genomics in everyday practice but there are many examples of how this is beginning to transform the way we look at diseases in terms of diagnosis, prognosis and treatment. The experience from oncology and other fields is helping cardiovascular medicine not only for investigating HF but the reciprocal nature of this can be clinically useful (for instance, predicting treatment responses) to drive laboratory investigations (teasing out the pathways in non-responders to treatments can be a focus of new drug discoveries).[9] As etiology of HF is far more complex than previously realized molecular assays such as gene based micro-arrays coupled with robust algorithm derived from newer bioinformatics tools will provide ample opportunities developing diagnostics and prognostics and also important therapeutics.[10] State of the art technologies are currently available to study genetics of CVDs, including mutation screening; genome wide association studies (GWAS) and the recently developed NGS. Genetic mutations of ion channel genes can lead to inheritance of SCD. Thus, further refinement in technology may aid in the development of molecular assays for detecting mutations and single nucleotide polymorphisms (SNPs) which have been shown to be linked with left ventricular hypertrophy (LVH). Also, hypertension (HTN) and obesity are well-established independent contributors for LVH pathology, but they only explain half of the variance of left ventricular mass (LVM) in humans. Clinical evidence suggests that there is a genetic basis to the observed inter-individual variability in the susceptibility for the development of LVH. Given the substantial relationship between LVM and cardiovascular events, elucidating the genetic determinants of inter-individual differences in the susceptibility to LVH is of considerable public health importance because it promises to identify high-risk individuals for targeted intervention and may identify novel targets for improved prevention and treatment.

Another cause of HF is the congenital heart defect (CHD), which is also a common cause of morbidity and mortality across countries representing a unique situation in both categorization and protocol management of HF. It remains unclear if the current guidelines for diagnosis and treatment of HF in adults can serve as a meaningful framework for these patients. Additionally, widely used conventional HF therapy of β-blockers and angiotensin converting enzyme (ACE) inhibitors has not demonstrated clear survival benefit and adequately powered and controlled randomized studies are lacking and remain challenging to conduct.[11] Genetic factors and subsequently acquired postnatal factors also play roles in progression to HF in CHD. Three possibilities that lead to HF in CHD are rare monogenic entities causing both CHD and HF; occurrence of severe CHD lesions in which acquired hemodynamic effects of CHD or surgery result in HF; and, most commonly, a combined effect of complex genetics in overlapping pathways and acquired stressors caused by the primary lesions.[12] Hypertrophy has generally been considered as a compensatory response to hemodynamic stress but evidence from patients and animal models suggests that it is a maladaptive process in response to intrinsic and extrinsic stimuli. Although hypertrophy can normalize wall tension, it is a risk factor for QT-prolongation and SCD. Studies using mice revealed many molecules are involved in hypertrophy and several critical pathways involved in the process were revealed. These are important advances in cardiology and together with functional genomics and proteomics could lead to more comprehensive approaches to prevent life threatening arrhythmia and SCD.[2,8,13,14]

Atrial fibrillation (AF), which results in stroke and HF is a constant concern in aging population. Because of its intermittent nature from distinct subtypes, diagnosing AF can be difficult. Due to our poor understanding of AF mechanisms, modification of cardiovascular risk profile is the only option. Better monitoring for electrocardiographic precursors of AF and the rapidly evolving field of investigative genomics are potential areas of future research which may provide insight underlying the AF substrates for preventive targets.[15] Sadly, prevalence of chronic HF (and AF) is increasing as a result of better surgical, medical and improved therapy management of CVDs. Since treatment options are unsatisfactory for arrhythmic conditions, systems biology approaches to enhance understanding of cardiac arrhythmias might offer possible options via an accumulation of large clinical datasets, application of NGS along with selected experimental and computer-based models. Such an approach may also facilitate the development and targeted applications of currently available therapeutics.[16] Similarly, long QT syndrome (LQTS) is lethal but a treatable cardiomyopathy via pharmacotherapy, device therapy and left cardiac sympathetic denervation (LCSD). Although a marked reduction in number of cardiac events is usually seen after LCSD, ≈50% of high-risk LQTS patients have experienced ≥1 post-LCSD breakthrough. Therefore, LCSD may not be viewed as curative or as an alternative in implantable cardioverter defibrillator (ICD) for high-risk patients. Interestingly, prophylactic LCSD may provide another choice to counter a suboptimal quality of life resulting from medication related side effects.[17]

DCM is the main cause of late manifestations of HF in heart transplantations. Importantly, a sizable percentage of DCM patients indicate genetic etiology. While molecular assays can identify people at risk, epigenetics and sentinel phenomics staging can also help patients. Functional genomics guided pharmacologic therapeutics matching patients' genetic architecture might inform us on as to what extent gene variation is involved in the neuro hormonal activation and its effect on HF. Treatment of chronic HF rests on hormonal paradigm and often includes ACE inhibitors; β-blockers and anti-aldosterone regimens which halt more than one hormonal system in HF.[18] Drugs such as Etomoxir which inhibit carnitine palmitoyl transferase-I increases glucose oxidation and enhances SERCA2 expression might be a good option for HF patients in this scenario.[19] Clinical studies concerning ACE polymorphism revealed significant relationship between the DD allele in ACE genome and increased mortality or need for heart transplantation. The risk turned out to be more in people without β-blocker treatment. Clopidogrel is ineffective in 10-30% of patients as the impaired activity of CYP3A4 enzyme in individuals is considered to be the reason for inadequate response. Use of the enzyme activators such as Rifampicin improves the outcomes. New generations of antiplatelet drugs such as Brilinta, which do not need to be converted to an active form was recently approved by food and drug administration (FDA) as a blood-thinning drug to treat acute coronary syndrome (ACS). Resistance to aspirin was proven in 5-10% of patients and 24% presented suboptimal response indicating the involvement of genetic components.[20] Studies on kinase

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signaling such as PKC-mediated phosphorylation of cytoskeletal, myofilament and mitochondrial proteins in the heart have provided some insight into the phenotypes of HF, hypertrophy and cardio protection. Also, proteomics study of the mitochondria revealed novel evidence for signaling cascades, some of which are known to involve various isoforms of PKC providing insight into the determinants of morphological as well as metabolic maladaptation, both in the heart and other tissues.[21]

An enormous number of proteins are present in cells. Sub-fractionation and the enrichment of specific organelles are emerging as important tools to understand the mechanisms underlying pathological phenotypes. Being a new system, the study of protein variations as a result of biological processes and perturbations can unravel unanticipated findings as proteomics field is currently undergoing transformation owing to the completion and annotation of human genome. This will potentially yield novel multiple biomarkers reflecting CVDs, establish earlier detection strategies and monitor responses to therapy in coming future since technological advances would permit the unprecedented large-scale identification of peptides in biological samples with mass spectrometry, where as gel-based assays can provide further refinement on the status of post translational modifications (PTMs).[22] In fact, application of high throughput protein evaluation with a subset of predefined targets, identified through proteomics, microarray profiling and pathway analysis in animal models and human tissues, is currently gaining momentum both in research and clinical applications. Proteomic analysis has already provided important insights into ischemic heart disease, HF and cardiovascular pathophysiology. The combination of proteomic biomarkers with clinical phenotypes and genetic haplotype information can surely lead to a more precise diagnosis and therapy on an individual basis, the fundamental premise of 'personalized medicine'.[23] Elucidation of the human genomic sequence was one of the greatest achievements of science and understanding the functional role of human genes and millions of polymorphisms was possible through a multidisciplinary approach using microarrays and bioinformatics. Variations occur in ~1% of human population and most of them are SNPs.[24] As we know, major CVDs such as MI, HF and CHD are a result of both genetics and environmental interactions. These area complex groups of diseases resulting from genetic predisposition and multiple environmental factors (infectious diseases especially viral ones can also induce drastic changes). As mentioned earlier, HF is leading cause of increasing hospitalization and its incidences are on rise adding to a significant burden on our health care. We believe that a systems biology approach to transplantation in HF patients encompassing genomic medicine approach can leadto better understanding of immune regulation post heart transplantation to minimize the graft rejection in patients.

Common forms of HF in the population are non-Mendelian and the current evidence points out that heritability is modest. In past, study of the genetic susceptibility to HF has been limited to patients with rare familial forms of HF and candidate gene association studies in patients with distinct subtypes of HF. Now, with availability of human genome sequence and the developments from the HapMap project, large-scale GWAS are feasibl[4] Further, as we make progress to discover novel biomarkers for diagnosis and prognosis in HF, the potential clinical utility of related clinical readouts such as renal insufficiency, should not be ignored, as renal involvement is fairly common in patients with HF, with both acute kidney injury and worsening renal functions being associated with poor prognosis. Thus, urinary biochemistry for searching potential biomarkers may even have advantages over blood analyses, including lower costs, better patient comfort and higher sensitivity to renal injury. Recent advances in proteomics have allowed identification of numerous urinary biomarkers, many of which show promise in HF populations.[25] In essence, understanding the complexity of sequence-structure-function relationships in HF is the primary goal and will require true advances in structural biology, proteomics and computational technologies.[26]

Large scale quantitative analysis of gene expression and proteomics is being applied to HF and atherosclerosis but is limited by variations in the platforms and gene products as well as sensitivity and specificity of the selected probes. Despite these challenges, the study of relationships between gene variation and biochemical phenotype (functional genomics) or response to medication (pharmacogenomics) during the long-term follow-up on clinical events should allow to study the prognostic importance of common genetic variants and plasma biomarkers. We know that the prognosis of HF is generally not good and in fact it is even worse than that of most cancers. But there is certainly a hope that new interventions such as well characterized homogeneous population of stem cells and other robust therapies might succeed in the fight against HF and novel drugs, based on thorough understanding of the system biology and 'omics' based science might make a cut in treating and preventing HF. Further, we must keep developing innovative animal models to drive insights into the complex mechanisms that cause hearts to fail. This type of endeavor would definitely accelerate newer drug discoveries for both the acquired and the inheritable CVDs. When feasible we must also try to compare genomics results with the existing data for respective protein activity such as zymograms, Western blots, 2DGE and immunohistochemistry as it can be highly reassuring in terms of reliability. Again, pharmacogenomics is going to be useful and will be routinely employed for evaluating prescribed drugs' efficacies. Interestingly, large-scale genomics will not only support but would also address newer drug discoveries which are also very important issues in cardiology. In a nutshell, the application of genomics, proteomics and metabolomics to HF will enhance our knowledge about different processes contributing to HF syndrome, thereby enabling the establishment of specific diagnostic profiles and therapeutic templates that could help improve the poor prognosis associated with HF.[27] Molecularly, changes in a failing heart are preceded and accompanied by specific gene expression (fetal-genes) alleged to the development of HF. Therefore, counteracting their expression could constitute a potential therapeutic approach.

Approval of BiDil by FDA in 2005 for treating HF in African-American was just the beginning of a whole new era of treating patients with specific vision. Since then researchers have come up with newer strategies regarding gender, race and ethnicity, age and the application NGS that can reveal novel ways to advance 'precision medicine' such as mechanism of action of future drugs and directions pertaining to genetic variation in one's genome. Finally, investigative genomics for unborn babies may become routine since we already have technologies to deliver information about future health based on one's genome to explore whether unborn babies might face health problems and be aware of preventive measures in advance that might benefit them. Thus, genomics can enable exome screening of clinically relevant and deleterious HF alleles that are paternally inherited or had arisen as *de novo* germ-line mutations making determination of the fetal genome to facilitate the diagnosis of most inherited and *de novo* genetic conditions.[28] Multiple causes and consequences of

HF make it an attractive proposition for analysis and treatment using latest advances in genomic medicine, especially where the failure is idiopathic in nature. Advances, such as NGS in relation to genomics and the developments in proteomics and also metabolomics as diagnostic services for detecting HF prone patients (who run a higher risk of developing HF symptoms in their life time) well before they have full blown pathological outcomes can ensure timely treatment and hence the well-being of our affected patients. However, as these advanced technologies develop further and become wide-spread, we must be aware of their capabilities, where each technology could be best applied and be sure that they have been analytically and clinically validated in relevant patient populations. Further, as the development outpaces practices, we must be mindful of ethical implications of these technologies, including their societal and economic impact, data interpretation challenges and of course patient's privacy and freedom.

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Conflict of interest

Author declares that there is no conflict of interest.

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