Genomics and the circulation

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From genetics to genomics

Between the elucidation of DNA sequence in 1953 and completion of the draft sequence of the human genome in 2001, the new discipline of genomics was born, studying the functions and interactions of all genes in a systematic fashion, including their interaction with environmental factors. Using large-scale experimental methodologies and statistical analyses, functional genomics aims to analyse the regulation of gene expression in response to changes in physiological parameters, whereas the goal of structural genomics is to determine the three-dimensional structures of proteins. The conceptual quantum leap from genetics to genomic medicine began with the identification of a variable stretch of DNA (i.e. a polymorphism) near the human β-globin gene associated with the sickle-cell mutation, followed by the suggestion that the location of genes could be predicted in given kindreds by their genetic linkage to a variant, equivalent to gene mapping. The advent of positional cloning in the 1980s gave a new boost to the task of identifying candidate disease genes, allowing the isolation and characterization of a gene once its location was approximately known without presupposing any information about the gene product. Using this strategy, roughly 1200 disease genes have been identified and characterized, among which many are associated with cardiovascular diseases. Although monogenic cardiovascular disorders are uncommon, elucidating the mechanisms by which single genes can cause disease has clarified our understanding of the molecular basis of human genetic diseases, leading to a better appreciation of the pathophysiology of more common cardiovascular diseases like atherosclerosis, coronary artery disease (CAD), hypertension and stroke, which are genetically complex. Such multifactorial (polycgenic, complex) diseases characteristically involve an interplay of many genetic variations of molecular and biochemical pathways and their interactions with environmental factors. Many rare genetic variants responsible for monogenic disorders exist in the human population, with these alternative forms of genes (i.e. alleles) typically being evolutionarily recent, highly penetrant (carriers of the mutant gene will likely have the disease), and inherited in simple mendelian fashion (hence, termed mendelian diseases). However, most of the genetic diversity in the population is attributable to more common alleles (i.e. with a frequency of >1% in the general population). According to the ‘common-variants/common-disease’ hypothesis, it is the common functional allelic variations that probably modulate individual susceptibility to common complex diseases, and the manifestation, severity and prognosis of the disease process. Indeed, the major challenges and ongoing research efforts facing the post-genomic period are to connect the nearly 36 000 genes of mammalian organisms to the genetic basis of complex polygenic diseases and the integrated function of complex biological systems. Genomic research has improved our understanding of all aspects of cardiovascular function, including molecular signalling, contractile mechanisms and energetics, vascular and myocardial structure and remodelling, and electrical activation and propagation. In addition to the identification and construction of single-nucleotide polymorphisms and haplotype maps of the human genome, genomic-based techniques such as high-throughput DNA and protein sequencing, DNA microarray chips for expression profiling, mass spectrometry and bioinformatics have been used to identify and validate targets for pharmacological interventions. In this review we describe the various strategies and technical aspects of genomic applications to cardiovascular disease, so that the limitations and potential of these methods can be clearly appreciated.

Genetic analysis of complex cardiovascular diseases

Significant effort has taken place with complex cardiovascular disorders to emulate the success that genetic analysis has had in explaining the nature of more rare...
single-gene (monogenic) cardiovascular diseases such as familial hypercholesterolaemia, hypertrrophic cardiomyopathy and long-QT syndrome. Most ongoing research on complex cardiovascular disorders focuses on identifying genetic variants (polymorphisms) that enhance susceptibility to given conditions. Often the design of such investigations is complicated by the presence of multiple risk factors, gene–environment interactions and a lack of even rough estimates of the number of genes underlying such complex traits. There are two general strategies for identifying complex trait loci. The candidate gene approach is motivated by what is known about the trait biologically, and can be characterized as a hypothesis-testing approach because of the biological foundation supporting the proposed candidate genes. The second strategy is a genome scan, in which hundreds/thousands of markers (also called anonymous polymorphisms) uniformly distributed throughout the genome are used to locate genomic regions that may harbour genes influencing the trait variability and to demonstrate the existence of trait genes with detectable effect sizes. This is a hypothesis-generating approach, allowing the detection of previously unknown trait loci.

Both the candidate gene and the genome scan approaches can be evaluated using one of two fundamental methods of identifying gene variants affecting common diseases: linkage analysis or association studies in human populations. These methods are defined below.

**Linkage analysis**

Linkage analysis is used to identify the chromosomal location of gene variants related to a given disease. This approach has been used successfully to map hundreds of genes for rare, monogenic disorders. New linkage methods are being specifically developed and tested for complex disorders since some of the basic assumptions of analysis of traits inherited in classical mendelian fashion are not valid. For example, the nature of complex diseases precludes the use of extended families under the hypothesis that the same disease allele acts in most affected individuals throughout a pedigree. Rather, in complex disease a multitude of genes with rare and/or common alleles creates an apparently chaotic pattern of heterogeneity within and between families. The overall effect of this, together with the potentially weak influence of many loci, is a heavy toll on the statistical power to detect individual contributing genes. This may be the reason why very few scans so far have yielded disease loci that meet genome-wide significance criteria. However, a few positive findings have emerged using this approach. Combining linkage analysis with advanced molecular genetic techniques, the chromosomal location (5q12) of a gene influencing stroke was identified, and risk of myocardial infarction was mapped to a single region on chromosome 14. In addition, successful mapping of many determinants of complex cardiovascular function in male rats has been reported, providing the first rough approximation of genome regions linked to homeostatic control of sodium and water excretion and arterial pressure. However, within these broad regions reside hundreds of genes that may act alone or in concert with each other to determine the relationship to the traits to which they segregate. Modifications to current methodology are in development, with the aim of increasing statistical power. Examples are the use of intermediate traits with potentially increased genetic homogeneity, the investigation of admixed populations and the study of linkage disequilibrium over wide genomic regions.

**Association studies**

As mentioned above, genetic effects on complex cardiovascular disorders are likely to involve multiple susceptibility markers of individually modest importance, thereby limiting the application of linkage analysis. Association studies examine the frequency of specific DNA variants in groups of unrelated individuals with disease and unaffected controls. The increased statistical power, and the fact that they do not require family-based sample collections, are the two main advantages of this approach over linkage analysis. Associations between polymorphisms in ‘anonymous’ genes derived by sequencing clones from human cardiovascular complementary DNA (cDNA; synthesized from an RNA template) libraries (hence, termed expressed sequence tags, ESTs), usually encoding proteins of unknown function, can be tested in affected and unaffected individuals using a case–control study design. However, most significant information has been gathered so far from association studies in which prior knowledge of the gene or its protein product existed. The candidate gene approach has been widely used to analyse possible associations between genetic variants and disease outcome, with genes selected because of a priori hypotheses about their potential aetiological role in the disease, based on current understanding of the disease pathophysiology. For example, polymorphisms within the renin–angiotensinogen system and nitric oxide synthase were tested for their association with hypertension. The renin–angiotensin system rapidly became the object of increased attention to identify genomic risk factors in hypertension. Similarly, the possible effects of these polymorphisms on genetic predisposition for CAD or restenosis after angioplasty have been extensively investigated. Recent twin studies report that the amount of variability in death from CAD that is attributable to genetic variability (i.e. its heritability) is as high as 0.58. Genetic factors associated with CAD mortality are in operation throughout the entire lifespan, although they seem to be particularly important at early phases of life, as manifested by a decrease in heritability with age. Recently, two large-scale association studies have identified gene variants that might affect susceptibility to myocardial infarction. Accumulating evidence suggests that specific genotypes are associated with organ-specific
perioperative outcomes, including neurocognitive dysfunction, renal compromise, vein graft restenosis, post-operative thrombosis and vascular reactivity, sepsis, transplant rejection and death (for a review, see Ziegeler and colleagues). A summary of the main association studies related to adverse perioperative cardiovascular outcomes is presented in Table 1.

One of the main weaknesses of the association approach is that, unless the marker of interest ‘travels with’ (i.e. is in linkage disequilibrium with) a functional variant, or the marker allele is the actual functional variant, the tests will have no power to detect and map complex trait loci. Other known limitations of genetic association studies include potential spurious findings resulting from population stratification (i.e. admixture of different ethnic or genetic backgrounds in the case and control groups) and multiple comparison issues in the assessment of candidate genes. The most reliable method of identifying a true relationship between genetic polymorphisms and disease is replication of findings across different populations or related phenotypes. Poor reproducibility in subsequent studies is one of the main criticisms of the candidate gene association approach. However, a recent meta-analysis identified that underpowered studies are the main contributor to the inconsistent replication, and proposed more stringent statistical criteria to exclude false-positive findings and the design of large collaborative association studies.

Large-scale gene expression profiling in cardiovascular disease

Focusing on the primary genetic defect using a reductionist approach to elucidate the causes of cardiovascular diseases has led to limited insight into the resultant complex pathophysiology, especially in terms of identifying novel therapeutic targets. However, our understanding of the molecular pathologies at work in cardiovascular disease is currently undergoing a paradigm shift as the need to describe the overall regulatory networks and interplay of different organ systems, cell types and even subcellular compartments and organelles has become apparent. This has led the scientific community to begin exploring and quantifying the transcriptome – defined as the assembly of messenger RNAs associated with the cellular response to stress and disease. At a cellular level, any injurious stimulus triggers adaptive stress responses determined by quantitative and qualitative changes in interdigitating cascades of biological pathways interacting in complex, redundant ways. Given these complex interconnections, the ‘single gene’ (or protein product) paradigm is insufficient to adequately describe, for instance, the myocardial response to severe systemic stimuli such as cardiac surgery with cardiopulmonary bypass. Instead, myocardial injury might better be defined by patterns of altered gene and/or protein expression, which can then be compared during disease development and over the course of disease progression. It is hoped that the integration of information from genome-wide differential expression profiling, at a variety of time points and phenotypes across different experimental conditions, with other types of genomic information will enable a better understanding of gene regulatory networks and their malfunction in cardiovascular disease. Although cardiovascular genomic analysis is most commonly focused on heart failure, its application to more acute settings, such as myocardial injury and protection, perioperative outcomes and the stress response of the pulmonary vascular system, is gaining popularity.

Table 1 Possible genetic basis for adverse perioperative cardiovascular outcomes. in/del, insertion/deletion polymorphism; ↑ increased; ↓ decreased; ↔ unchanged or increased; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; APCR, activated protein C resistance; NO, nitric oxide; PAI, plasminogen activator inhibitor; IL, interleukin.

<table>
<thead>
<tr>
<th>Gene name (symbol)</th>
<th>Polymorphism</th>
<th>Intermediate phenotype</th>
<th>Perioperative outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin I converting enzyme (ACE)</td>
<td>in16del/ins</td>
<td>del = ↑ enzyme activity</td>
<td>Perioperative blood loss, vascular reactivity, cardiac mortality/morbidity after CABG</td>
</tr>
<tr>
<td>β2-adrenoreceptor (ADRB2)</td>
<td>R16G</td>
<td>G16,Q27 = ↑ receptor downregulation</td>
<td>Major adverse cardiac events, death after cardiac surgery</td>
</tr>
<tr>
<td>Chymase A (CMA1)</td>
<td>in16del/ins</td>
<td>in16 del = ↑ enzyme activity</td>
<td>Vein graft occlusion after CABG</td>
</tr>
<tr>
<td>Coagulation factor III (tissue factor) (F3)</td>
<td>-1208del/ins</td>
<td>-1208ins = ↑ TF level</td>
<td>Early first CABG</td>
</tr>
<tr>
<td>Coagulation factor V (F5)</td>
<td>R506Q (Factor V Leiden)</td>
<td>Q506 (FV Leiden) = APCR</td>
<td>Primary renal allograft thrombosis, stroke, bleeding after cardiac surgery</td>
</tr>
<tr>
<td>Endothelial NO synthase (NOS3)</td>
<td>E298D</td>
<td>D298S = NO generation</td>
<td>Coronary spasm, enhanced response to phenylephrine on CPB</td>
</tr>
<tr>
<td>Integrin, beta 3 (platelet GPIIIa) (ITGB3)</td>
<td>L33P (Pl A1/PlA2)</td>
<td>Pl A2 = sensitivity to activation; platelet aggregability; fibrinogen binding</td>
<td>Myocardial injury and death after CABG</td>
</tr>
<tr>
<td>IL6</td>
<td>-174G/C</td>
<td>-174C, -572C = ↑ IL6 level</td>
<td>Inflammatory response after cardiac surgery</td>
</tr>
<tr>
<td>PAI-1</td>
<td>-572G/C</td>
<td>4G = ↑ PAI-1 level</td>
<td>Vein graft thrombosis after CABG</td>
</tr>
<tr>
<td></td>
<td>-675(5G/4G)</td>
<td></td>
<td></td>
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Several methods are currently in use for large-scale gene expression profiling, including differential display, EST identification and sequencing, serial analysis of gene expression (SAGE) and microarray analyses using either cDNA- or oligonucleotide-based chips. Of these, microarray technologies have revolutionized the analysis of gene expression changes in biological events and in complex diseases by simultaneously examining the expression of many thousands of transcripts in a single experiment. Computational analyses of the vast amounts of data thus generated include special algorithms that enable the identification of global patterns of gene expression and grouping genes into expression clusters. Investigating the relationship between such clusters of candidate genes provides greater insight into their potential biological relevance to cardiovascular diseases than simple comparisons of up- and downregulated genes. Below, we offer a brief overview of microarray studies that have helped to decipher some of the transcriptional regulatory networks underlying cardiovascular disease.

Genomic approach to heart failure

Congestive heart failure represents the final common pathway of almost any disease or injury that results in cardiac cell and tissue damage. Initial events such as myocardial infarction, hypertensive pressure overload or inflammation result in the activation of remodelling processes, defined as genome expression, and molecular, cellular and interstitial changes manifested clinically as changes in the size, shape and function of the heart after cardiac injury. While being a homeostatic adaptive response at first, sustained cardiac hypertrophy and remodelling may over time become maladaptive, eventually leading to heart failure. The progression from compensated cardiac hypertrophy to decompensated heart failure is accompanied by marked changes in the expression of a host of genes preferentially expressed in the myocardium. Identifying possible aetiological and specific markers for early cardiac decompensation and progression to end-stage heart failure represents the target for genomic-based studies.

Numerous investigators have used microarrays or other large-scale expression profiling technologies, such as subtractive hybridization or genecalling to elucidate transcriptional profiles in experimental models of myocardial infarction, myocarditis and various ventricular hypertrophy models. Differential expression patterns have also been identified in myocardial samples from heart failure patients (end-stage hypertrophic, ischaemic and dilated cardiomyopathies). While comparison of these results is difficult because of differences in the technology used, experimental conditions, data analysis and tissue types, some consensus can be found. Examples include induction of the atrial and brain natriuretic peptide (ANP and BNP) genes and extracellular matrix genes in cardiac hypertrophy, and induction of genes involved in stress response, inflammation and wound healing in different models of myocardial infarction. Novel sets of differentially expressed genes, previously not implicated in the disease under study, are being identified. The number of genes expressed in the cardiovascular system has been estimated at between 21 000 and 27 000, and cardiovascular-based cDNA arrays (CardioChips) have been developed to facilitate the identification of cardiac-specific genetic markers. Of note, the high end of the estimated number of genes expressed in the cardiovascular system is very close to the full complement of genes encoded by the entire genome. This supports the idea that the majority of genes in the human genome are involved in the normal maintenance and physiology of an organ regardless of its specific function, while only a small proportion are allocated to cell-specific functions. Determining and cataloguing such tissue-specific gene expression profiles in response to different stimuli to the heart will lead to the accumulation of a compendium of cardiac gene expression. This can be subsequently used to develop new disease classification systems and to identify the diverse targets affected by a therapeutic intervention. Identified genes of interest can be added as possible ‘unbiased’ candidate genes to enhance future association studies. However, before such use, quality assurance protocols are required to validate microarray results. These include experiment replication, selection of cut-off values used to identify differentially expressed genes, and confirmation of results by alternative methods (quantitative reverse transcriptase polymerase chain reaction, northern blotting or in situ hybridization). Finally, every new hypothesis has to be further tested through either gain- or loss-of-function studies in biological systems (such as transgenic overexpression, dominant-negative, antisense or gene targeting strategies), in order to establish a causal relationship of the change in gene expression with the disease – one gene at a time.

Genomic approach to myocardial ischaemia and cardioprotection

Several studies have profiled myocardial gene expression in the ischaemic heart, demonstrating alterations in the expression of immediate-early genes such as c-fos, junB and genes coding for calcium-handling proteins (calsequestrin, phospholamban), extracellular matrix and cytoskeletal proteins. Subtractive hybridization – an unbiased method for detecting transcriptionally and post-transcriptionally regulated genes – was used to analyse expression patterns in stunned myocardium and identified upregulation of transcripts associated mechanistically in cytoprotection (heat shock proteins), resistance to apoptosis and cell growth, as well as previously uncharacterized genes.
Microarray technology has also been utilized in the quest for novel cardioprotective genes, with the ultimate goal of devising strategies to activate these genes and prevent myocardial injury. Preconditioning is one of the well-studied models of cardioprotection, which can be induced by diverse triggers including intermittent ischaemia, osmotic or redox stress, heat shock or toxins. Although acute preconditioning does not require new gene synthesis, delayed preconditioning depends on enhanced transcription of genes that lead to cardioprotection. The main functional categories of genes identified as potentially involved in cardioprotective pathways include a host of transcription factors, heat shock proteins, antioxidant genes (superoxide dismutases, haem-oxygenase, glutathione peroxidase) and growth factors. Results from transgenic studies have also suggested that, depending on the level and duration of expression, certain genes (e.g. protein kinase C-epsilon) can have either myocardial protective or hypertrophic effects. A preliminary step in elucidating which genes are causally involved in cardioprotection would be to determine patterns of genes expressed in a coordinated manner that are shared across different models of cardioprotection, for example preconditioning, endogenous protection (male/female differences) or transgenic animals.

Genomic approach to atherogenesis

Several studies have analysed gene expression profiles in different types of human atherosclerotic lesions or in cultured cells and animal models of atherogenesis using cDNA microarrays. Results have validated genes already known to be involved in the atherosclerotic process (e.g. apoE, TIMP, CD68), and identified sets of novel differentially expressed transcripts (e.g. ICAM-2, PIM-2, ECGF 1). Genes potentially involved in rupture of human atherosclerotic plaques (e.g. peripherin) have been detected using subtraction hybridization and microarrays.

Activation of vascular smooth muscle cells followed by proliferation and migration are the key pathophysiological factors in the development of post-angioplasty restenosis, vein graft failure and transplant arteriopathies. Specific genes expressed in activated human smooth muscle cells, graft neointima and stenotic aortocoronary vein grafts have been described using large-scale gene expression profiling methods. Such changes in gene expression underlie both adaptive and pathophysiological responses that allow vascular cells to remodel, form new vessels or progress to apoptosis. A set of differentially expressed genes in aortic media as compared with vena cava media has been identified using cDNA microarrays, adding to the understanding of molecular phenotypic differences between arteries and veins. Also, a number of genomic-based studies have focused on alterations in vascular gene expression in response to various biomechanical perturbations (shear stress, pulsatile flow). A summary of these studies separated by specific vascular wall cellular components is presented in Table 2.

Limitations of gene expression profiling

Although newer Affimix high-density oligonucleotide microarrays (GeneChip) contain more than 39 000 transcript variants, a major limitation of the microarray technology remains the limited number of genes present on the array, and the fact that genome-wide chips are still unavailable for most species. In studies utilizing tissues made up of heterogeneous cell populations, analysis tools must be used to unpick the tissue complexity, or isolation of cell types must be performed in a manner likely to preserve in vivo expression patterns. For example, a recently developed technique called laser-capture microdissection allows very small cell populations or even single cells to be dissected. Most importantly, expression studies alone cannot prove function. The transcriptome is not fully representative of the proteome (the complete complement of proteins encoded by the genome), since many transcripts are not being actively targeted for translation, as evidenced recently with the concept of gene silencing by RNA interference. Furthermore, alternative splicing, post-translational modifications and protein–protein interactions responsible for biological function remain undetected. Finally, integration and comparison of results is difficult, especially across species and platforms. To address this

Table 2. Cell-specific vascular gene expression studies. cDNA, complementary DNA; SAGE, serial analysis of gene expression; LDL, low-density lipoprotein; LPS, lipopolysaccharide; NO, nitric oxide

<table>
<thead>
<tr>
<th>Vascular cell type</th>
<th>Stimulus</th>
<th>Platform</th>
<th>Findings/references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial cells</td>
<td>Shear stress</td>
<td>cDNA microarray</td>
<td>Downregulation of pro-inflammatory and fibrotic pathways; upregulation of survival, angiogenesis, matrix remodelling; regulation of NO synthesis</td>
</tr>
<tr>
<td>Cyclic strain</td>
<td>Oligo microarray</td>
<td>SAGE</td>
<td>Upregulation of pro-apoptotic genes</td>
</tr>
<tr>
<td>Oxidized-LDL</td>
<td>SAGE</td>
<td>SAGE</td>
<td>Endothelial cell activation genes</td>
</tr>
<tr>
<td>Tumour-associated</td>
<td>SAGE</td>
<td>SAGE</td>
<td>Upregulation of matrix remodelling, cell migration-adhesion-interaction genes</td>
</tr>
<tr>
<td>Smooth muscle cells</td>
<td>Mechanical strain</td>
<td>cDNA microarray</td>
<td>Regulation of matrix remodelling and vasomotor genes. Synthesis of proteoglycans</td>
</tr>
<tr>
<td>Macrophages</td>
<td>LPS</td>
<td>SAGE</td>
<td>Activation of cell migration, angiogenesis, remodelling and inflammatory pathways</td>
</tr>
<tr>
<td>Oxidized-LDL</td>
<td>cDNA microarray</td>
<td>SAGE</td>
<td>Downregulation of cell cycle progression genes, induction of nuclear receptors</td>
</tr>
<tr>
<td>Mechanical strain</td>
<td>cDNA microarray</td>
<td>SAGE</td>
<td>Upregulation of early response genes</td>
</tr>
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problem, the National Heart, Lung, and Blood Institute (NHLBI) has launched the Programs of Genomic Applications (PGA), to develop information, tools and resources to link genes to biological function on a genomic scale, in order to advance scientific research related to heart, lung, blood and sleep disorders (http://www.nhlbi.nih.gov/resources/pga/). In spite of their limitations and only when coupled with richly annotated comparative databases, DNA microarrays have the potential to become useful tools in cardiovascular disease classification, prediction of treatment responses and prognosis, and identification of novel therapeutic targets.

**Genome–Proteome–Physiome/Cardiome–Phenome**

The Human Genome Project provides the sequence of nucleotides, localization of genes and amino acid sequence in encoded proteins. However, less than 5% of the human genome represents DNA whose sequence ultimately encodes a protein. Although regulatory sequences and boundaries between the coding (i.e. exons) and non-coding (i.e. introns) regions of the genes are now being recognized and investigated, reaching the goals of functional genomics would require detailed knowledge of regulatory networks of gene expression as well as developmental and metabolic pathways. As mentioned above, microarray studies have revealed that many concurrently regulated genes share the same biochemical pathway and that cellular states may be associated with distinct and unique transcriptional profiles. These studies have provided a framework on which proteome analyses are based. Proteomics complements genome-based approaches by enabling the identification and characterization of differential protein expression, turnover and localization, post-translational modifications (e.g. addition of sugar moieties or lipid attachments to a protein), and interaction with other biological molecules, thus providing new insights into the complex cellular processes involved in cardiovascular dysfunction. To this end, several human cardiac protein databases have been established, and proteome analyses in various human cardiomyopathies and animal models of heart disease have been reported. The potential for ‘protein chips’ to function as versatile and rigorous high-throughput methods for proteomic analyses is the object of intense investigation. Other more recent functional genomic and proteomic approaches include protein–protein, protein–DNA or other ‘component–component’ interaction mapping (interactome), systematic phenotypic analyses (phenome) or transcript or protein three-dimensional localization mapping (localizome). To overcome the intrinsic limitations of all individual ‘omic’ approaches, integration of data obtained from several distinct approaches using systems biology strategies has been proposed. This may lead to better functional annotations for the gene products and functional relationships between them, and allow the formulation of relevant biological hypotheses, which can subsequently be tested using either synthetic biology or mathematical modelling of complex signalling networks. Such integrative approaches to specifically study cardiovascular function (the Cardiome Project) have already been outlined. Furthermore, the cardiovascular community needs to wrap the profiling data within the biological phenomenology, the so-called ‘phenome’ in which the model under study is completely characterized in terms of the changes at the cellular, biochemical, organ and system level (Fig. 1).

**Conclusion**

Future trends and challenges in cardiovascular genomics are still being defined, but mainly concern interdisciplinary studies designed to combine an analytical system approach, mathematical modelling and engineering principles with the molecular and genetic factors and stimuli and the macro-scale interactions that determine cardiovascular function. This may in turn lead to a personalized approach towards medicine and preventative health care. Genomic and proteomic approaches are rapidly becoming platforms for all aspects of drug discovery and development, from target identification and validation to individualization of drug therapy.

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148