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Family studies throughout the 1970s and 1980s documented the role of shared genetic factors in the familial aggregation of cardiovascular disease and its risk factors, including hypertension. These familial aggregation studies, however, do not identify and characterize the role of particular genes. Identification of the genes contributing to interindividual variation in disease risk may facilitate early identification of patients who are at elevated risk of cardiovascular disease before the onset of any clinical symptoms, development of more efficacious treatments by exploiting previously unidentified metabolic and physiological pathways, and the tailoring of particular treatments to patients who are most likely to respond on the basis of their genetic constitution.

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Cardiovascular disease risk and risk factor levels are controlled by complex interactions among numerous metabolic and physiological systems, as well as demographic and lifestyle factors. Because so many systems are involved, variation in a large number of genes can potentially influence interindividual variation in disease risk, and the impact of any one gene is likely to be small to moderate in size. Before the current revolution in genomic analyses, studies identifying genes contributing to cardiovascular disease risk were of 2 basic types: studies of rare inborn errors of metabolism and association studies of a priori biologic candidate genes. The former have proved very useful for the identification of novel pathways, but the frequencies of these conditions are very rare, so their contribution to the prevalence of disease in the general population is minimal. The latter have proven useful in a few cases, such as the apolipoprotein E polymorphism with plasma cholesterol levels and risk of myocardial infarction, but have been plagued by lack of consistency. Modern genomic analyses have provided 2 additional pathways to identify genes that may be contributing to disease risk: gene expression profiles and genome-wide linkage analyses. Nothing further will be presented in this editorial on gene expression arrays except to state that they represent a comple-
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Steps for following up genome-wide linkage scan, including fine mapping, gene resequencing, association studies, and functional assays. After identification of gene and functional allele, efforts will rapidly turn to detailed analyses of positional candidate genes. If no strong positional candidate genes are evident, fine mapping will rely on identification of SNPs throughout the linked interval for surveys by association/linkage analyses. This exercise may be greatly facilitated by public and private efforts to generate and make available a large number of SNPs distributed at high density throughout the genome. After SNPs that show associations in large population-based samples are identified, the investigator must identify which gene contains or is nearby the associated SNP or combination of SNPs. The process of identifying genes, although daunting only 1 or 2 years ago, is greatly facilitated by the burgeoning human DNA sequence data and sophisticated bioinformatics tools.

The second step is to identify the complete menu of DNA sequence variation within the identified genes through DNA resequencing or other methods (the Figure). Contrary to misunderstandings in the popular press and loose writing in the professional literature, a prototype sequence of the human genome does not exist for any individual. Rather, the sequence of the human genome is different among each and every one of us (except perhaps monozygotic twins), and this interindividual variation is a key contributor to differences in disease risk and their response to medical treatment among individuals, families, and populations. Like the gathering of the original sequence of the human genome, DNA resequencing will likely take place with existing technologies and has, in fact, already begun. Because of the possibility that variation within noncoding regions may influence the regulation of gene transcription and other functions, DNA resequencing should not be limited to only the protein-coding regions of the gene but rather should include 5’ and 3’ regulatory regions, as well as introns.

The third step is to identify those variable sites (or combinations of sites) identified by resequencing that are influencing the traits of interest. This is typically carried out by genotyping the variable sites in large population-based samples to identify sites that show association or linkage with the appropriate phenotypes. It is this third step that we are least prepared to competently accomplish because we lack an agreed-on conceptual and analytic framework to relate the large amount of DNA sequence variation that exists in modern human populations with interindividual phenotypic variation in a sample of moderate size, although promising developments are emerging. After polymorphic sites that show association or linkage with relevant phenotypes have been identified, the fourth step is to demonstrate functional effects on gene expression or protein function. In general, these studies will require experimental cellular and animal models to directly measure the effects of naturally occurring DNA sequence variation. As is often the case, the apolipoprotein E polymorphism can serve as a paradigm for such functional studies. The functional laboratory, however, will not be limited to cellular and animal models; it must also include the population in which the ultimate impact on disease and the interactions with the environment will be elucidated.

The report by Rice et al and several other recent examples are early ripples in a tidal wave of studies to localize genes for cardiovascular disease and its risk factors. Sequencing of the human genome by both public and private efforts is rapidly progressing, as is the identification of sequence variation. It is therefore imperative that similar progress be made to place the onslaught of information in the context of improving the human condition. Both consumers and providers of health care should stop thinking of genetic risk profiles as distant science fiction and begin a constructive dialogue as to how they may benefit patient and public health. In addition, appropriate protections need to be implemented so that genetic risk profiles are not used to discriminate against individuals and obstruct access to appropriate health care. Because of its common prevalence in the population, availability of successful prevention and treatment regimens, and traditional leadership in contemporary biomedical research, the heart and vascular diseases are ideally suited to lead the effort for translating advances in genome research to the betterment of health care and human health.

References


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Peeking Under the Peaks: Following Up Genome-Wide Linkage Analyses
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