Contemporary Approaches to Gene Discovery
Progress Toward Personalized Medicine?

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It is broadly recognized that cardiovascular disease has a familial basis; however, progress in identifying the causative genes has been slow. The goal of identifying disease genes or those genes influencing cardiovascular risk factor phenotypes is at the heart of personalized medicine, giving rise to the hope that such knowledge will identify new therapeutic targets, help identify individuals at high risk to receive interventional therapy, and perhaps help to refine prognosis once clinical disease is present. Testing of candidate genes and genome-wide searches using anonymous, highly polymorphic markers via linkage studies has produced some information regarding the location of putative trait genes but has left open the question of precisely which genes are at play, which are the relevant variants, and how they function to modify disease risk. The advent of high-density arrays, in which up to a million single-nucleotide polymorphisms can be assessed in thousands of subjects in a cost-effective manner, has opened the door to an unprecedented level of inquiry. Much finer mapping information can be obtained because this approach relies on linkage disequilibrium, which extends over much shorter distances than does linkage.

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There is currently vigorous activity in almost all domains of complex human diseases to apply genome-wide association scans (GWAS) to identify trait loci. In this issue of Circulation: Cardiovascular Genetics, Ding and Kullo review the basic tenants of this approach and the progress that has been made toward gene discovery in the area of atherosclerotic heart disease. The review is an excellent introduction to the approach and will set the stage for further reading and study for those interested. Although some significant progress has been made, as noted in the article, there remain significant challenges including interpretation of the results in the context of a huge multiple testing problem, power, and sample sizes necessary to detect variants of modest effect, and heterogeneity that thwarts attempts at replication. Moreover, the marker map available for study is geared toward detection of common variants, either directly measured in the genotyped panel or in linkage disequilibrium with a measured marker. Thus, less common variants (<1% frequency) are not expected to be identified with this approach, at least with current technology. The limitations of the approach should not overshadow the fact that new discoveries have been made, paving the way for follow-up studies to characterize the functional variants, their physiological or metabolic effects, and their role in integrated pathways. Certainly, GWAS will produce a whole new set of discoveries; however, by itself, it is not likely to solve the issue of the genetic underpinnings of complex human diseases, as evidenced by the observation that the variants already identified account for only small proportions of the total trait variation.

One of the applications of gene discovery to advance the goal of personalized medicine is to enable the development of predictive indexes of disease outcome on the basis of genotypes. In another article in this issue, Ioannidis evaluates the feasibility of creating such indexes using the published results of GWAS studies. This is a reasonable evaluation, as the imperative to translate recent discoveries into clinical practice is strong. Not surprisingly, Ioannidis finds that clinical use of associated markers to improve cardiovascular risk prediction is premature. There are a number of reasons for this. As already mentioned, the variants identified by GWAS account for only small proportions of trait variance; in general, common variants tend to have smaller effect sizes than do rare variants. Furthermore, the functional status of the associated variants is generally unknown. The single-nucleotide polymorphisms evaluated in GWAS are generally not in exons, and on some platforms, have been selected simply to capture the common haplotypes within a linkage disequilibrium block; thus, a priori, they are not likely to be functional variants. It is possible that more careful mapping by resequencing and characterization of the actual functional single-nucleotide polymorphisms may have substantially better predictive value. Furthermore, a GWAS is fundamentally a tool that operates under the “common variant, common disease” hypothesis. There are a number of studies and consortia assembling large sample sizes (some published having 30 to 50 000 subjects and others in the works will include 100 000 subjects) for meta-analysis, ensuring sufficient power to detect common variants accounting for as little as 0.05% of the trait variance at genome-wide significance levels, depending on sample size. If there are common variants influencing complex traits, these studies will surely find them. However, if rare variants with heterogeneity, epistatic interactions, or interactions with environ-
mental triggers are important, much of the trait variance may remain unexplained. It is important to take Ioannidis’ conclusion in this context: predictive indexes on the basis of current knowledge of associated variants in this early stage of discovery are premature, resulting in weak predictive models. However, the dream of personalized medicine and predictive indexes may yet be achieved, but it seems it will take far more than these first steps on the road to gene discovery. This is a topic that surely should be revisited once efforts toward gene discovery, identification of functional variants and pathways, and searches for less common variants allowing for heterogeneity have progressed.

Nonetheless, this is an exciting time in biomedical science, with the technical ability to delve into genomic variation at this level of detail, and there will be remarkable discoveries.

But as one might imagine, this paradigm will not solve all questions regarding the genetic underpinnings of complex human traits. Our journey is just beginning.

Disclosures

None.

References


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