Loosening the Cuff
Important New Advances in Modeling Antihypertensive Treatment Effects in Genetic Studies of Hypertension
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Human hypertension is a common, chronic disease associated with serious cardiovascular and renal co-morbidity and with substantial social and economic costs. It is therefore important to understand the genetic basis of this disease. The investigation of genetic determinants, and particularly the search for specific susceptibility loci, is likely to be essential to the understanding of disease pathogenesis. Identification of specific genes regulating variation in blood pressure will allow fundamental insights into the pathogenesis of hypertension and will in turn help to better define epidemiological risk factors. The characterization of major genes modulating risk of hypertension and the consequent derivation of improved risk estimation will assist in building the foundation for long-term programs of epidemiological and clinical investigation and intervention. Progress toward these goals holds the potential for enormous public health benefits.

The study of familial aggregation is the first step in investigating the genetic basis of any disease. Description of familial aggregation of the disease state and associated phenotypes provides circumstantial evidence for a genetic component to etiology and paves the way for extended genetic investigations. Variance components analysis, the engine for the descriptive genetic epidemiology of quantitative traits, attempts to partition observed variation in a quantitative trait into genetic and nongenetic components. Variance components analysis, such as that undertaken by Cui et al, is an essential tool in phenotype definition and in exploring the complex pathogenic pathways leading to disease. Variance components models can easily be extended to genotype-phenotype analyses and form the basis for several linkage methods.

Challenge of Mapping Susceptibility Loci for Hypertension
Mapping human susceptibility loci for hypertension is likely made difficult by a high population frequency, incomplete penetrance, phenocopies, genetic heterogeneity, and possible epistasis and pleiotropy. Replication of any positive results may be difficult, and often the significance of different findings among studies is controversial. Although significant progress has been made in defining the genetic basis of hypertension and normal variation in blood pressure in the last decade, even large studies are likely to have had low power to map genes of modest effect by linkage. Considerable effort is currently being expended in attempts to detect genetic loci contributing to hypertension susceptibility. However, clinical hypertension is a complex, heterogeneous phenotype with a variable age of onset and has proven extremely difficult to dissect genetically. In common with many other complex diseases, multiple whole genome scans for hypertension in different populations have not generated regions of consistent linkage. Similarly, consensus areas have failed to emerge from genetic association studies.

Modeling Antihypertensive Treatment Effects: A Particular Concern
There are many possible reasons for lack of replication of linkage or association findings or failure to detect common genes. Potential interpopulation heterogeneity in study design, phenotype definition, genetic structure, environmental exposures, and markers typed may play a large role in nonrepeation. Limitations in study design, including underpowered studies and a failure to attempt explicit replication, coupled with positive publication bias and a tendency to overinterpret marginal results, may also play an important role. However, one significant analytic limitation has been a consistent failure to appropriately deal with subjects on antihypertensive treatments. Appropriately modeling the effect of antihypertensive treatment on systolic and diastolic blood pressure is a particular issue for studies of hypertension. Antihypertensive treatment is a form of censoring, with treated individuals having "censored" values because of the effects of treatment. Genetic studies of hypertension almost invariably include individuals on antihypertensive treatment because of the high prevalence of the disease and the widespread use of pharmacotherapy. Exclusion of treated individuals has been the most common method for dealing with possible treatment effects in genetic studies. However, simply ignoring the treatment effect or excluding medicated individuals has been shown to result in substantive reductions in evidence of linkage. It is intuitive, as it is logical, that subjects contributing to the upper range of variation in blood pressure contribute important information for genetic studies.

The fundamental aim of genetic epidemiological disease research is to define causal factors increasing disease risk.
Hypertension and the physiological traits associated with hypertension exhibit non-Mendelian patterns of inheritance and substantial heterogeneity. The many pathogenic pathways involved in the clinical expression of hypertension suggest that disease results from the action of multiple genetic and environmental determinants. However, the pathogenic mechanisms underlying clinical hypertension are very intricate and are likely to include elements of the metabolic syndrome, obesity, and cardiovascular risk factors. Informed genetic analysis and clearly defined phenotypes will not be possible until the basic mechanisms and interactions underlying these pathophysiological factors are understood. An important piece of the puzzle lies in understanding the effects of treatment on blood pressure and in developing appropriate analytical methods for dealing with treatment effects. Lack of a standardized approach to dealing with blood pressure measures in treated individuals has greatly impeded progress toward defining the genetic basis of hypertension.

New Approaches to Modeling Antihypertensive Treatment Effects

Cui and colleagues describe an investigation of various ways of dealing with antihypertensive treatment in genetic studies of blood pressure in the overall context of variance components analyses of pedigree data. Using an exceptional community-based family resource from Australia, the Victorian Family Heart Study, they compared various approaches to the treatment issue for systolic pressure: using measured pressures for treated subjects, excluding treated subjects, substituting the relevant 95th percentile values for treated pressures, and adding a constant of 10 mm Hg to treated pressures. Cui et al report that adding a sensible constant to the BP measures of those subjects on antihypertensive treatment maximized the genetic component of variance relative to other possible corrections, such as using the relevant 95th percentile BP values or excluding those on treatment from the analyses. They also show that subjects on treatment add valuable information and concomitant power to genetic analyses. These findings represent an important methodological advance and will enable researchers to access more of the information contained in family or population-based samples for the study of hypertension genetics. New analyses made possible by these analytic tools are likely to result in improved power to study the genetics of blood pressure variation and hypertension, and perhaps in an increased ability to detect loci of modest effect and to replicate findings among genetic linkage and association studies.

The findings reported by Cui et al introduce some important new concepts for the analysis of blood pressure in epidemiological and genetic studies. There remains much work to do in further investigating the effects of treatment on variance components analyses and on power to detect susceptibility loci for hypertension in linkage and association studies. The issue of treatment effects will be of particular interest in gene-environment studies of hypertension. We are in the midst of a genomics revolution, and evolving genomic technologies are increasingly making possible new understanding in hypertension and cardiovascular disease. However, this study reminds us forcefully that molecular methods alone are generally insufficient for dissecting complex pathogenic pathways or for localizing genes modulating susceptibility to complex human disease, and it emphasizes the value of the close integration of methodological research in statistics with gene discovery efforts.

References

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