Can Genomic Medicine be Applied to the Management of Essential Hypertension?

Philip F. Giampietro, MD, PhD, Medical Genetics Services, Marshfield Clinic, Marshfield, Wisconsin

In this issue of Clinical Medicine & Research the paper by Dr. Friedrich Luft,1 “Mendelian Forms of Human Hypertension and Mechanisms of Disease” nicely outlines diagnostic clues to aid the practitioner in the recognition of monogenic forms of hypertension in clinical practice. This paper identifies a series of six causative genes for well-defined genetic syndromes that act at different steps of the renin angiotensin system. His paper stresses the importance of obtaining a family history for clues about associated conditions (Neurofibromatosis Type 1, Von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2) in other family members and noting early ages of onset of hypertension in affected individuals. This would raise suspicion that a patient’s hypertension may have a single allele genetic basis and indicate the need for a physical examination to identify phenotypic abnormalities.

However, at the present time our understanding of the genetic factors involved in the development of essential or idiopathic hypertension, i.e., hypertension with no definable cause, is progressing, but less clear than the monogenic forms of hypertension that have been identified to date. Essential hypertension represents the most common (>90%) category of hypertension and the most important health problem in developed countries. Clinical evidence indicates that essential hypertension accounts for a heterogeneous category which has different subtypes including low-renin and high-renin essential hypertension. Most studies support the hypothesis that essential hypertension is caused by a combination of genetic and environmental factors, namely a multifactorial etiology.

The treatment for hypertension is imperfect. Medication prescription tends to be nonspecific and is associated with side effects and non-compliance. The National Heart, Lung, and Blood Institute (NHBLI) in “The Seventh Report of the Joint National Committee on Prevention” stated that most patients with hypertension will require more than one drug to control their hypertension. Because of associated morbidities including end stage renal disease and congestive heart failure there is certainly incentive enough to improve our understanding of gene and environmental interactions that contribute toward the development of essential hypertension.
There are at least 100 candidate genes for human essential hypertension that play a role in the renin angiotensin system, adrenergic system, kallikrein kinin system, steroid system, salt-water homeostasis, metabolism, vascular structure and tone. During the past decade, our understanding of the arrangement of the 30,000 genes which are responsible for the development of *Homo sapiens* has been advanced by the Human Genome Project. Attempts to “tease out” a subset of these candidate genes that could be involved in the pathogenesis of essential hypertension have been attempted through an approach called “genomic-wide scan” (GWS). This approach relies on statistical association studies that are performed using nuclear families or sib-pairs. One study by Levy\(^2\) identified chromosome 9 as a region for diastolic blood pressure and several regions on chromosomes 5, 10 and 17 for systolic blood pressure. Based on several lines of evidence in humans and rats, the region on chromosome 17 has been further narrowed to 17q12-21.

There are limitations to the use of GWS. Negative results for candidate gene regions may represent “false negative” results if the patients in the sample analyzed had heterogeneous causes for their hypertension. Other loci with a small influence on blood pressure may not be identified. It has been proposed\(^3\) that “intermediate” patient phenotypes in the hypertensive population need to be identified based on measurable biochemical parameters in order to stratify hypertensive patients into more homogeneous groups for candidate gene testing. Once causative genes are identified, the possibility of developing new drugs to treat different etiologies of essential hypertension can be explored.

One of the many applications of the Human Genome Project is the incorporation of “genomic medicine” in clinical practice.\(^4\) Genomic medicine involves the utilization of functions and interactions of all genes in our genome in order to develop improved medical care for many common medical conditions. Our present knowledge regarding susceptibility loci for essential hypertension is limited. To obtain clinically relevant information careful epidemiologic studies need to be designed in order to identify genotype-disease associations.\(^5\) Appropriate intervention strategies based on genotype need to be tried and validated. When trying to extrapolate findings from one population to the next, it is important to take into account the ethnic structure of each population. Clinical practice guidelines for the implementation of genetic susceptibility testing will need to be developed with attention to ethical, legal and social issues.

In medical practice today, practitioners need to rely on clinical means of identifying patients at risk for developing hypertension and monitor patients according to appropriate guidelines. Hypertension has been identified\(^6\) as one of 18 common medical conditions in which knowledge of a positive family history can be utilized to initiate appropriate prevention strategies. Based on family history a person can be placed in a population, moderate- or high-risk category for a particular disease. Identification of family members with early onset of hypertension should raise suspicion for the possibility of a genetic contribution in the development of hypertension. Since family history is influenced by genetic susceptibilities as well as common environmental exposures shared by family members, a proactive use of a patient’s family history is one crucial means by which practitioners may begin to practice “genomic medicine” for management of essential hypertension as well as many other “common” medical conditions encountered in clinical practice.

REFERENCES