Hypertension Highlights

Geneticism of Essential Hypertension

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The idea that a person’s genetic constitution is all-important and that genetic knowledge is sufficiently advanced so that we can make judgments on our past or future health was called geneticism by Medawar. He termed geneticism as the application to the human condition of a genetic knowledge or understanding that is assumed to be very much greater than it really is. Proponents of geneticism have promised us that the sequencing of the human genome will offer limitless insights into the pathogenesis of essential hypertension and, moreover, will provide bountiful access to new drug targets and facilitate pharmacological therapy. In terms of citations, only “hypertension and sodium” provokes more “hits” than “hypertension and genetics.” Nevertheless, with a few exceptions, the results appear disappointing. We might pause and reflect on the answers to the question, “Why?” In so doing, we should first examine the genetic differences that separate us from one another. The genetic differences between human beings seem to be of 3 types: those based on single gene mutations, those based on polymorphic genetic differences, and those resulting from a complex interaction of many genes.

First, there are the differences that divide us into a great majority and a tiny minority. Essential hypertension clearly does not involve a tiny minority and not yet a great majority; however, this state-of-affairs was lost on early students of the subject. When Weitz first proposed the notion of genetic variance on blood pressure, he concluded that essential hypertension was inherited through the actions of a single gene. Because essential hypertension is common, were Weitz correct, we would expect 2 distinct blood pressure distributions in the population, the haves and the have-nots. Indeed, that very argument occupied Platt and Pickering. Platt studied family histories, measured blood pressure in normotensive probands, hypertensive propositi and their relatives, and argued as Weitz did. Pickering et al, however, studied systolic and diastolic blood pressure distributions from the second to eighth decades in first-degree relatives of normotensive and hypertensive probands. They found that the frequency distribution moved upward as age advanced. At no age was there a clear-cut blood pressure distribution into normal and high blood pressures. Moreover, others found subsequently that the relationship between blood pressures of parents and sons was linear for both probands and propositi. As a matter of fact, the relationships were no different than those for height. Pickering concluded that blood pressure is inherited as a graded character over the entire blood pressure range, whether this value is regarded as hypotension, normotension, or hypertension. Nevertheless, disorders that separate us into the great majority and the tiny minority indeed exist. Methods to elucidate these monogenic disorders are at hand and a series of these hypertensive (or hypotensive) disorders have been elucidated. However, nearly all of us are lucky enough not to have one of these disorders; the great majority of us are neither carriers of one of these gene mutations nor victims of its action.

There are many genetic characteristics that do not divide human beings into a huge majority and a tiny minority. This second form of genetic variability divides us into distinct classes of which none is a huge majority or a tiny minority. Examples are blood groups, A, or B, or AB, or O, or minor blood groups or histocompatibility loci. Variations of this kind are described as “polymorphic.” Polymorphisms are common variants, generally not too important clinically, but not necessarily trivial. Some students of genetics can recall the professor who determined who in the class could taste phenylthiourea. The professor may have also concerned himself with those persons in the room whose urine stank after eating asparagus compared with those whose urine did not. Those of us who were trained in medicine before the advent of proton pump inhibitors will recall that persons with type O blood type have a higher risk for duodenal ulcer, whereas those with type A blood type are more prone to coronary disease. Determining blood group polymorphisms is highly worthwhile before starting a blood transfusion. Polymorphisms do not exist by accident. One possibility is that an advantage exists for the population to be subdivided into 2 or more distinct groups, which depend on and thereby sustain each other. The extreme example might be the sexes. The basis of this polymorphism has been built into our genetic structure for a long time. It would be very “impolitic” for me to argue that one or the other form of this polymorphism is superior. However, negative aspects of the Y chromosome in terms of cardiovascular risk are well known. Suffice it to say that the possibility has been raised that the Y polymorphism (the whole chromosome) is likely to die out in the future, leaving the solely X individuals to enjoy the world for themselves.
A species may benefit from the heterozygosity of polymorphisms. In cardiovascular disease, the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism (Alu repeat in intron 16) that, for still unclear reasons, is associated with low, intermediate, or high concentrations of the enzyme may be an example. Persons homozygous for the I allele are said to be more successful at mountain climbing, whereby those homozygous for the D allele might be more successful at withstanding salt-free, dehydrating circumstances. Thus, our species has by virtue of heterozygosity for this polymorphism the option of moving to Katmandu or crawling across the Gobi desert. Selection would then determine which polymorphism is successful. Indeed, the maligned D allele, accused of heart disease, hypertension, and a host of other ills, was associated with longevity in 2 studies, raising the possibility of pleiotropic, age-dependent effects for this polymorphism.

Several thousands of articles have been written on hypertension and polymorphisms. The ACE I/D gene polymorphism is responsible for >1000 papers alone. The poor polymorphism is incriminated in arteriosclerosis, ventricular hypertrophy, response to altitude and exercise, hypertension, pre eclampsia, rheumatic mitral valve disease, vesico-ureteral reflux, hypertension, pulse pressure, fibrinogen levels, renal disease progression, rheumatoid arthritis, stroke and its severity, and Alzheimer disease, to name just a few. The promise that ACE polymorphisms are a guide to ACE inhibitor therapy was laid to rest in a recent negative study. Polymorphisms in the angiotensinogen gene are a distant second place at ~500 “hits.” The T174 mol/L-M235T polymorphisms that are in linkage disequilibrium with a variant in the gene’s promoter have been the most incriminated. The variants have an influence on angiotensinogen levels. Some authors believe that these variants may be responsible for 1.5 to 3.0 mm Hg variance in blood pressure, although that point is disputed. Recently, a “dosage” effect was postulated for the M235T polymorphism. However, in my view, the final word on the angiotensinogen polymorphisms has been published. The promoter single nucleotide polymorphisms alone or as haplotypes did not predict the continuous variables of systolic, diastolic, or pulse pressure in cross-section or the risk of ischemic heart disease or ischemic cerebrovascular disease in either gender in case-control or prospective studies. Individuals with 6AA, 174TT, or 235TT in the angiotensinogen gene had increased plasma angiotensinogen levels and moderately increased risk of elevated blood pressure (women only), but unaltered blood pressure examined as a continuous variable and unaltered risk of ischemic heart disease and ischemic cerebrovascular disease. Because the study relied on data from 10,690 persons, it cannot be dismissed on the basis of a trivial sample size. The same group subsequently published a meta-analysis of 127 trials and determined that the angiotensinogen M235T genotype was associated with a stepwise increase in angiotensinogen levels in white subjects and a corresponding increase in risk of hypertension in both white and Asian subjects. A company has offered genotyping-happy customers a “salt-sensitivity” test on the basis of this polymorphism (caveat emptor!). But perhaps the “little polymorphism that could” is the 825T allele of the GNB3 gene. The allele is said to be predictive of enhanced Gi protein activation and in that way could influence the activity of G protein-coupled receptors. The polymorphism was incriminated in hypertension, diabetes, and obesity in rapid succession. Subsequently, a host of other undesirable conditions have followed. Recently, a longitudinal study of 461 persons observed over the course of 5 years suggested that individuals with the 825T allele progressed to hypertension more rapidly than those who did not. Perhaps the only happy note is that an increased response to sildenafil occurs in those carrying the 825T allele.

Particularly alluring are polymorphisms that demonstrate counterparts in experimental animals. The cytoskeletal protein adducin that influences the sodium pump is ideal in that regard. The Milan salt-sensitive rat features an adducin variant that may contribute to salt sensitivity. Evidence from human subjects demonstrated polymorphisms in an adducin gene that could in part explain salt-sensitive hypertension and responses to thiazide diuretics. Unfortunately, detailed family studies could not confirm the general usefulness of adducin. In some studies, several polymorphisms have been tested simultaneously. For instance, diuretic response is said to be predictable when one considers both the ACE I/D polymorphism and adducin. In the Atherosclerosis Risk in Communities study, the adducin gene variants and GNB3 were tested simultaneously. In this study, GNB3 came up short but adducin showed some association with peripheral vascular disease. Perhaps it is a bit unfair to expect GNB3 and adducin to explain hard cardiovascular end points, when we are just beginning to investigate these polymorphisms in terms of blood pressure regulation. A host of other polymorphisms in genes encoding enzymes, receptors, signaling proteins, and the like have been tested and incriminated in hypertension, which cannot be detailed here.

The fact that other investigators do not commonly replicate genetic association studies involving polymorphisms led to an anonymous editorial in which the author outlined sensible criteria for such studies. The criteria included biological plausibility, low probability values, independent replication, rigorous phenotypic assessment and genotyping, and appropriate statistical analysis. Other editorialists published commentaries with similar conclusions. Subsequently, Ioannidis et al conducted a meta-analysis of association studies. They included 370 studies addressing 36 genetic associations for various outcomes of disease. The investigators found that the first study usually showed a stronger genetic effect than subsequent studies. Both bias and genuine population diversity explained why early association studies tended to overestimate effects. Others have reached similar conclusions and have underscored that associations of polymorphisms with complex diseases are at best hypothesis generating; however, the studies say little about the role or function of the gene. The resources that have been poured into genetic association studies have been considerable. Some ask, “Has the cost been worth it?”

An alternative approach to testing candidate genes by association is the effort to find “new” genes responsible for hypertension. The technique used linkage, which has the advantage that no preconceived notions are made concerning
the gene involved. A major drawback is the fact that linkage provides information solely on location, “where is it,” and not on “what is it.” Linkage has been superb in enabling us to find the genes responsible for monogenic conditions. For complex genetic disease, however, linkage has been disappointing. Despite incredible effort with the genotyping of 3599 members of sibling pairs, the Medical Research Council-funded British Genetics of Hypertension (BRIGHT) study was able to identify only a single locus on chromosome 6 with some promise of significant linkage.\(^\text{19}\) Even less productive in terms of linkage evidence was the National Heart Lung and Blood Institute-funded Family Blood Pressure Program (FBFP) study. That study did provide other interesting insights, including the fact that leukoariosis, white matter lesions, show a strong genetic influence.\(^\text{20}\)

To my knowledge, no hypertension gene has been found for essential hypertension by virtue of a linkage analysis in humans or animals. As a matter of fact, linkage studies for any complex trait have yielded less than modest results. Harrap has attempted to explain these disappointing results.\(^\text{21}\) He points out that the distribution, number, and behavior of alleles might be responsible. He divides the gene seekers into “lumpers” and “splitters.” The lumpers believe or hope that a few common, probably ancient, alleles exert substantial influence on the genetic variance of blood pressure.\(^\text{22}\) The splitters favor the common disease, rare allele hypothesis. The latter hypothesis implies that blood pressure alleles come from a larger number of younger, less frequent, and more population-specific alleles. Perhaps Harrap could have added the “grumblers,” the politest form of fighters known, who reason that a few ancient alleles probably exert trivial effects on blood pressure and that rare alleles are just that. Perhaps, when we move to linkage disequilibrium mapping with single nucleotide polymorphisms (SNPs) numbering in the hundreds of thousands, rather than relying solely on several hundred microsatellite markers, we will learn more. In any event, the prospects are daunting and do not inspire confidence in additional total genome scans for essential hypertension.

The third way by which human beings may differ genetically from one another are complex, quantitative traits. Our height, body mass index, cholesterol, blood pressure, or performances on standardized tests, if you like, are examples already recognized by Galton. “Hypertension is a characteristic such as height,” concluded Pickering.\(^\text{2}\) Height and blood pressure are clearly heritable, as a myriad of twin studies have shown. Presumably, numerous or many genes act in concert to determine the phenotype. For this reason, we call these disorders polygenic. We are under considerable pressure to think of polygenic disorders as if they were just a highly complicated form of simple segregative inheritance, Mendelism on a grand scale, or, if you will, a “symphony orchestra” model. However, to my knowledge, the symphony orchestra model has not been shown convincingly scientifically and exactly how polygenic traits work remains to be determined. Another consideration is the complex interaction of networked genes with environmental stimuli. The environment exerts pressures for genetic change that are occasionally not gentle. Gene flow is subjected to evolutionary “bottle necks” and all of humankind did not invariably move through the same bottles until recently. As we all move through the “Big Mac–Kyoto Accords” bottle, we can observe how type 2 diabetes develops in some of us with a body mass index of 22 (Indian subcontinent) whereas others first reach that achievement (United States and Europe) with a considerably higher body mass index. We now know that all genes feature single nucleotide polymorphisms every 1000 base pairs or so. Some are in coding regions. Others lead to amino-acid substitutions and are termed “nonsynonymous” for that reason. However, it would be erroneous to conclude that synonymous single nucleotide polymorphisms or single nucleotide polymorphisms in introns have no meaning. The fact of the matter is that we do not know for certain.

Guyton, Coleman, and associates provided us with the first comprehensive computerized model of blood pressure regulation.\(^\text{23}\) More than 30 years ago, they examined an entire series of blood pressure regulatory mechanisms experimentally. They conducted comprehensive reviews of all additional available information. They constructed a series of differential equations to define the interactions between these mechanisms. They concluded that regulatory mechanisms operated either short-term, for intermediate periods, or long-term, thereby exhibiting infinite gain. In the Figure is shown only an excerpted <10\% (circulatory dynamics) of the schema they suggested. If we examine this schema today, its complexity is daunting. Nevertheless, in the past 30 years we have identified other regulators that Guyton et al\(^\text{2}\) could not foresee. These regulators include natriuretic peptides, aminoguanidines, nitric oxide, endothelin, urotensin, and novel eicosanoids, to mention only a few. The host of hormones, other mediators, receptors, signaling molecules, and neural and humoral effectors clearly suggest that a few alleles in a handful of genes are not likely to explain increased blood pressure.

My associates and I made an attempt at dealing with lipid metabolism as a complex trait. Compared with hypertension, lipid metabolism is a “no brainer.” Low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL) can be easily measured, are relatively constant, and can be sent through the mail, in contrast to blood pressure measurements. LDL, HDL, and the ratio of LDL/HDL are recognized risk factors. We established a mathematical model analogous to that constructed by Guyton et al for lipid metabolism. We recruited a cohort of >1000 persons in 250 families over 3 generations so that we had grandparents, parents, and adult children in the study. All were phenotyped for LDL, HDL, and LDL/HDL ratio. We were able to estimate the effect of genetic variance on the phenotypes based on the family structures and arrived at a value somewhat <50\% that was estimated by twin studies. We next genotyped 6 lipid-relevant genes, LDL receptor, lipoprotein lipase, hepatic triglyceride lipase, cholesterol ester transfer protein, apolipoprotein E, and lecithin acyl transferase to determine whether common haplotype variants in these common lipid metabolism-relevant genes predicted genetic variance on the phenotypes. They did.\(^\text{24}\) We then expanded this analysis to 7 additional genes. With common single nucleotide polymorphisms in 13 genes, we were able to construct haplotypes that account for approximately two-thirds of the...
genetic variance for LDL and HDL. Interestingly, we are able to account for almost all the genetic variance in the clinically relevant LDL/HDL ratio. These findings give us some grounds for optimism in terms of tackling complex genetic traits. However, lipid metabolism is a trivial academic pursuit compared with blood pressure. One glance at Guyton's schematic framework is sufficient to convince even the casual observer.

Where should we go to achieve genetic answers? Inheritance is the *sine qua non* of genetics. Mendel, Galton, Bates, Delbrück, Medawar, and other giants not mentioned here, all felt that way. In that case, which genetic model is likely to be successful? Family studies, in which people are related to one another, rather than sole case-control association studies would appear to be a more powerful tool. Cohorts from North Karelia, Iceland, Europe, Australia, and elsewhere might help us here. Family studies and particularly twin studies have much to offer in the study of complex quantitative traits, particularly in estimating the genetic and environmental components. A recent study of 767 adult nuclear families that included monozygotic and dizygotic twins showed that genetic and shared environmental components accounted for 46% and 31% of the total variance in systolic blood pressure, respectively. The method also permitted modeling antihypertensive treatment effects. Can the genetics of blood pressure regulation and essential hypertension be solved? I am not certain, but if we do not try, we will never know.

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**References**


