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A Review of Critical Hypertension Genetics

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ABSTRACT: ***Genetic variables have a role in the development of primary hypertension, according to family studies. The shift from this phenomenologic-biometric to a molecular-genetic approach, however, is more challenging. The dissecting of the poligenic complex of hypertension is based on the premise that the individual genetic variations underpinning the ocular hypertension must be more common in hypertensive patients compared to controls and should cosegregate with hypertensive in families. In the so-called monogenic type of hypertension, the validity of these assumptions was convincingly established. However, because of the complex network of feedback mechanisms that regulate blood pressure, it's conceivable that the same gene variation may have opposing effects on blood pressure depending on genetic and environmental factors. Independent sets of data addressed in this study (acute BP response to saline infusion, incidence of hypertension in a 9-year follow-up population, age-related changes in BP) point to a favorable answer to this issue. As a result, the effect of a particular genetic variation on blood pressure must be assessed in the context of the relevant genetic epistatic interactions. In a group of individuals with the right genetic and environmental circumstances, a negative result or a small genetic impact in the general population may become a large gene effect.***

KEYWORDS: ***Association, Blood Pressure, Essential Hypertension, Genetics, Linkage.***

1. INTRODUCTION

Hypertension, represented as blood pressure measurements of 140/90 mmHg or greater, affects an estimated 20–30 percent of the adult population in western society, but is a significant contributor to morbidity as well as cardiovascular disease mortality which include stroke, myocardial infarction but also end-stage renal disease. Essential hypertension, defined as elevated blood pressure without any apparent reason, comprises approximately 95 percent of all hypertension cases. In the other 5 percent of instances, the etiology of hypertension is secondary to diseases such as primary hyperaldosteronism, Cushing's syndrome (excessive glucocorticoids), pheochromocytoma or renal disease; it may also be drug-induced. The illness is believed polygenic, arising from the accumulation and combination of a variety of incremental genetic hazards. The manifestation of these hazards relies on interaction with environmental variables such as excessive food consumption of salt, alcohol, obesity and stress[1].

Two main methods are used to map genetic variations that affect illness risk: linkage analysis as well as association studies. These may be deployed by utilizing the genome-wide or the candidate gene approach. Until recently, genome-wide scans were done by linkage alone, while association studies generally focused at candidate genes. This is no longer true, since recent genome-wide association studies have already proved their value. In reality, complicated characteristics like hypertension or diabetes are attractive targets for this approach and initial findings are expected to be published this year.

1.1.Genome-wide linkage study in hypertension:

Genome-wide linkage analysis has been one of the major methods utilized in recent years to look for blood pressure control genes and hypertension susceptibility. This approach includes the genotyping of hundreds of polymorphic markers distributed evenly throughout the entire genome in families with many afflicted relatives (or multiple relatives in whom a characteristic has been assessed) (or multiple relatives in whom a trait has been measured). Markers that segregate with the illness (or characteristic) in relatives more frequently than

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anticipated are used to narrow down the location of the disease gene. The analysis is based upon a logarithmic odds ratio (Lod score) which indicates the probability of linkage divided by the likelihood of non-linkage[2].

1.2.Candidate gene approach:

Candidate alleles are chosen from systems physiologically involved in blood pressure control, e.g., the renin–angiotensin systems (RAS) or the adrenergic system. Association studies examine the allele frequency of a polymorphic marker, or even a collection of markers, between unrelated patients (cases) as well as healthy controls to find markers that vary substantially between the two groups. These studies have considerably higher ability to identify the impact of common variations. For population-based case-control studies, it is important that the cases and controls are selected from the same population and that there is no danger of ethnic heterogeneity that could produce a genetic artifact. Ethnicity is especially significant, since the representation of various genetic polymorphisms is very varied across ethnic groups. This may lead to misleading results in the study of common illnesses like essential hypertension[3].

1.3.Genetic variations of the renin–angiotensin system:

The RAS is known to affect all elements of blood pressure regulation including blood vessel contraction, salt balance, and cell growth in the heart. Significant efforts have been made towards the knowledge of the RAS and its significance in the regulation of blood pressure. Several polymorphisms of genes related to the RAS have been effectively associated with essential hypertension; however conflicting results have also been reported. Angiotensin-converting enzyme (ACE) is another well-studied component of the RAS. Elevated ACE levels were observed in individuals with heart failure as well as animal studies have shown that the ACE gene is linked with blood pressure. Conflicting findings were reported on the association of the ACE variants with hypertension, and two meta-analyses were unable to establish an independent association of the ACE I/D polymorphism with hypertension[4].

1.3.1. Adrenergic system:

The adrenergic system affects cardiac output, vascular tone, renal salt reabsorption and renin release. It is thus an ideal system from which to generate candidate genes for hypertension since it has been linked in the increased vascular reactivity seen in hypertensive patients.

1.3.2. Endothelial nitric oxide synthase gene:

The endothelin system, which consists of a number of strong vasoconstrictor peptides and receptors, is potentially essential in the regulation of blood pressure. Nitric oxide synthase (NOS) synthesizes nitric oxide from L-arginine. Nitric oxide is a key component of vascular relaxation. Studies exploring NOS polymorphisms with essential hypertension have so far produced conflicting or inconclusive findings. A recent meta-analysis of 35 genetic association studies that investigated the connection between essential hypertension and NOS SNPs only showed evidence for relationship with a polymorphism in intron 4 (4a/b) and hypertension in a recessive model. No relationship could be found in research including East Asian or black individuals[5], [6].

1.4.Animal models:

The rat has become the rodent model of choice for investigating hypertension, given the paucity of suitable inbred mouse models. There are 10 hypertensive inbred rat strains, each bearing combinations of characteristics found in human essential hypertension. The spontaneously hypertensive rat and the Dahl salt-sensitive rat have, in particular, been widely utilized for investigating the genetic basis of hypertension. One research utilizing the Sabra

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rat hypertension model of salt sensitivity revealed connection of two loci on chromosome 1 of the rat genome with the hypertensive phenotype. Gene expression profiles were produced from the rat kidneys, since it was believed that this organ was closely engaged in salt homeostasis. The researchers identified seven genes that overlapped between the QTL and gene expression studies. Although this is animal research, it offers a strong method for investigating human disease biology when useful tissues are not easily accessible.

Another intriguing component which may be important for human essential hypertension. Sex-specific variations in essential hypertension are usually ascribed to the involvement of sex steroid hormone-receptor systems attenuating sex-common disease processes in premenopausal women. The authors found sex-specific QTL in Dahl salt-sensitive/jrHS intercross rats with salt-sensitive hypertension. Although sex-common QTL were identified for blood pressure, most QTL across the three traits examined were gender-specific. Five QTL for blood pressure were identified in females, while three distinct QTL were found in men. Furthermore, interacting loci with substantial linkage were identified exclusively in female F2 intercross rats for blood pressure and hypertensive renal illness. Comparative investigations showed concordance of blood pressure. Altogether, these findings offer important experimental grounds for sex-specific study of causes and intervention and preventive methods for essential hypertension in people.

2. LITERATURE REVIEW

Timberlake et al. studied about Efforts to find high blood pressure genetic loci have mainly centered on candidate gene methods, in which particular candidates were examined for linkage and correlation with blood pressure related hypertension diagnosis. The renin-angiotensin-aldosterone framework, Sodium epithelial channel, catecholaminergic/adrenergic function, renal kallikrein system, -adducin, as well as others involved lipoprotein metabolism, hormone receptors, and growth factors have all been studied as potential genes. These investigations, as well as other genome-wide scans conducted more subsequently, have produced very promising findings, pointing to a number of possible candidate genes or genomic areas that may play major part in blood pressure variance. The findings also indicate to the need for stronger robust intermediate phenotypes in the pathogenetic development of hypertension[7].

Gimenez-Roqueplo et al. studied about in developed nations, essential hypertension is a significant cardiovascular risk factor. Many family investigations have shown its hereditary nature: approximately 30% of blood pressure variation is believed to be genetically driven. The identity of the culprit gene mutations, however, has been complicated by a number of factors, including the large number of genes with difficult-to-appreciate effects, the numerous genetic polymorphisms of each gene studied, and the critical role of environmental factors (diet, physical activity, etc.) on blood pressure or the effect of the genes that control blood pressure. The hunt for genes has centered on large case control studies and/or studies of siblings with hypertension, with the exception of certain uncommon caricatural types of Mendelian transmitted hypertension. With these groupings of topics, there are two basic methods. The first is examining so-called "candidate" genes, which code for proteins with recognized functions that may affect blood pressure. Many potential genes have been evaluated in the past 10 years, with mixed findings. The second method is to do a full genome screen without any previous knowledge. These more recent investigations have shown conflicting findings as well. The findings thus far show the difficulties of genetic study of a complex characteristic and the need for more integrated approaches: analysis of polymorphism combinations, analysis of phenotypes under controlled environmental circumstances, and investigation of gene-environment interactions[8].

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Chen et al studied about matrilineal inheritance is seen in mitochondrial DNA. Familial mitochondrial disorders caused by mtDNA mutations usually affect organs that use a lot of energy, such as the heart, brain, as well as skeletal muscle. It was recently shown that certain essential hypertension patients had traditional maternal inheritance, confirming and enlarging the role of mtDNA mutations as one of the molecular processes causing maternally inherited hypertension. However, there are still a number of more broad and fundamental issues that need to be addressed. The significance of mtDNA mutations in maternally inherited hypertension is discussed in this article, which covers current advances in mitochondrial genome evolution, mtDNA genetics, as well as the role of mtDNA mutations in maternally inherited hypertension[9].

Barlassina et al studied about Genetic variables have a role in the development of primary hypertension, according to family studies. The shift from this phenomenologic-biometric to a molecular-genetic approach, however, is more challenging. The dissecting of the poligenic complex of hypertension is based on the premise that the individual genetic variations underpinning the ocular hypertension must be more common in hypertensive patients compared to controls and should cosegregate with hypertensive in families. In the so-called monogenic type of hypertension, the validity of these assumptions was convincingly established. However, because of the complex network of feedback mechanisms that regulate blood pressure, it's conceivable that the same gene variation may have opposing effects on blood pressure depending on genetic and environmental factors. Independent sets of data addressed in this study (acute BP response to saline infusion, incidence of hypertension in a 9-year follow-up population, age-related changes in BP) point to a favorable answer to this issue. As a result, the effect of a particular genetic variation on blood pressure must be assessed in the context of the relevant genetic epistatic interactions. In a group of individuals with the right genetic and environmental circumstances, a negative result or a small genetic impact in the general population may become a large gene effect[10].

3. DISCUSSION

Essential hypertension is a complex disease that results from the interplay of susceptibility genes and environmental variables. It affects more than 20% of the adult population. To find hypertension susceptibility genes, researchers employed a variety of methods. This study focuses on current attempts to unravel the genetics of essential hypertension. More chromosomal regions containing blood pressure loci have recently been discovered in genome-wide linkage studies. The results of a novel two-dimensional genome scan, as well as sex-specific regions related to hypertension in inbred mouse models, are reported. Many case-control studies have been conducted, but the findings have been ambiguous thus far. The scientific community is shifting away from single-snp association studies and toward more sophisticated haplotype-based association analyses. This phase requires bigger sample numbers, but it will undoubtedly improve the association method by lowering the percentage of false positives. Finally, genome-wide SNP-based screening is now feasible, allowing us to assess numerous gene loci while taking epistasis into account. Indeed, geneticists are eagerly anticipating the findings of the first genome-wide association studies for hypertension or blood pressure using HapMap data, which are expected to be released in 2007. Our joint goal is that by identifying positive genes for essential hypertension, we will be able to better forecast individuals at risk, as well as create novel therapies and more precisely target their usage.

Until recently, significant advances in our understanding of the mechanisms of blood pressure regulation arose from studies of monogenic forms of hypertension and hypotension, which identified rare variants that primarily alter renal salt handling. Genome-wide

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association and exome sequencing studies over the past 6 years have resulted in an unparalleled burst of discovery in the genetics of blood pressure regulation and hypertension. More importantly, genome-wide association studies, while expanding the list of common genetic variants associated with blood pressure and hypertension, are also uncovering novel pathways of blood pressure regulation that augur a new era of novel drug development, repurposing, and stratification in the management of hypertension. In this review, we describe the current state of the art of the genetic and molecular basis of blood pressure and hypertension.

Blood pressure (BP) level is determined by just 2 variables: peripheral vascular resistance and cardiac output, but it exhibits a Gaussian distribution in the general population indicating that it is the net effect of a multitude of independent factors each with a small cumulative effect (this can be extended to hypertension which is a dichotomization of the quantitative BP trait.). Individuals with BP at the higher end of the BP distribution have been noted to have a higher risk of stroke and cardiovascular disease as early as 2600 BC. Understanding the complex nature of BP regulation accelerated after William Harvey description of the circulatory system in the 17th century, with each incremental advance reinforcing its multifactorial basis, and highlighted by Guyton iconic computer model of circulatory (BP) control in 1972 which incorporated empirically tested concepts of blood flow autoregulation and the pressure–natriuresis relationship.

In 1960, Paige proposed the Mosaic Theory of hypertension, which brought together interactions among genetics, environment, adaptive, neural, mechanical, and hormonal perturbations as the basis of hypertension. Until now the development of drugs to reduce high BP resulted from the more parsimonious model for blood pressure (a product of peripheral vascular resistance and cardiac output) rather than from the dissection of the complex genetic and physiological pathways involved. The major classes of antihypertensive drugs in current use act either as vasodilators or diuretics, which reduce peripheral vascular resistance and cardiac output, respectively. But the complexity of BP regulation means that current antihypertensive drugs, which all have a single site of action or target, can result in unpredictable and wide-ranging BP responses in individuals. The holy grail of hypertension research is neutralization of the excess cardiovascular risk posed by high BP. Among the scientific tools used to realize this goal is genomic research, based on the principle that identifying genes and genetic variants that influence the regulatory or counter-regulatory pathways of BP control will lead to the development of novel drugs and targeted treatment that will reduce high BP effectively without any adverse effects.

4. CONCLUSION

Methods deployed for dissecting genetics of complex diseases complement one another. Linkage analyses have been very popular over the last few years, but the association approach has regained popularity with the recognition that linkage analyses have proven largely unsuccessful for complex traits, that is for identifying common alleles with modest effects. The science community is now turning from the simplistic single SNP association to more complex haplotype-based association studies. This step requires larger population sizes, but will most certainly strengthen the association approach by reducing the proportion of false-positives. Finally, it has now become possible to perform genome-wide SNP-based screening, thereby enabling us to evaluate multiple gene loci in consideration of epistasis. Indeed, geneticists are keenly awaiting the first genome-wide association studies for hypertension or blood pressure utilizing the Hap Map information first results may be published in 2007. Our collective hope is that by finding positive genes for essential

hypertension we will be better able to predict those at risk and also, perhaps most importantly, to develop new treatments and to target their use in a refined way.

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