Invited review

Genetic factors in hypertension

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Abstract

The genetics of essential hypertension has proven refractory to molecular and epidemiological genetic approaches despite the early successes in identifying the genes involved in rare monogenic forms of hypertension. The problems facing the genetic studies for hypertension are not unique, but phenotypic characterization, heterogeneity and high prevalence make it a special case requiring a more individualized approach. We describe the current status of hypertension and blood pressure gene mapping strategies and summarise the key evidence for rare and common variants in the causation of hypertension. We explore intermediate phenotypes and pharmacogenetics as efficient strategies which have the potential to produce clinically translatable discoveries. The global health impact of hypertension is considerable and by understanding the genetic factors elevating blood pressure it may be possible to develop enhanced strategies for diagnosis, prevention or treatment.

Key words: hypertension, genetics, monogenic, blood pressure, heritability, candidate gene, pharmacogenetics, common disease common variant.

Systemic blood pressure (BP) is determined primarily by cardiac output and total peripheral resistance which are controlled by a complex network of interacting pathways involving renal, neural, endocrine, vascular and environmental factors. From an epidemiological and clinical perspective, BP at the higher end of the normal population distribution is associated with an increased risk of cardiovascular mortality and morbidity. Traditionally cardiovascular risk assessment is based on a predefined threshold at which the quantitative BP phenotype in converted into a binary trait (hypertension) and management strategies are directed towards BP reduction below this threshold at which the risk of excess cardiovascular events is abolished. From a genetic perspective, whether BP is considered as a quantitative trait or a dichotomous disease phenotype has major implications on studies of genetic causation. Revisiting the 1950s debate between Platt and Pickering on this subject [1] is a useful exercise to understand the assumptions that have driven genetic research of hypertension so far. Platt's argument that hypertension was a qualitative abnormality would suggest that hypertension is simple Mendelian disease and subject to the classic Mendelian laws of inheritance

exhibiting recessive, dominant, or codominant inheritance attributed to a single genetic *locus*. Platt reached this conclusion by studying family histories and measuring BP in normotensive and hypertensive probands and their relatives. On the other hand, Pickering studied systolic and diastolic BP distributions from the second to eighth decades in first-degree relatives of normotensive probands and hypertensive propositi and concluded that BP was inherited as a "graded character", and is hence a complex non-Mendelian trait [1, 2]. The term "complex trait" refers to any phenotype that does not exhibit classic Mendelian inheritance attributed to a single gene and result from the interactions between multiple genes and environmental factors. The distribution of BP in the population is a normal unimodal distribution which supports the complex multifactorial basis of BP regulation [3-5]. On this basis, essential hypertension which is a dichotomization of the quantitative BP trait can also be considered as a complex trait. However Platt's view should not be discounted entirely. Even though a bimodal distribution of BP as expected from Platt's theory is not observed, there are rare monogenic syndromes of hypertension and hypotension in a small minority of the population.

Magnitude of genetic component to the blood pressure phenotype

Familial aggregation of BP traits is demonstrated by family studies demonstrating correlation of BP among siblings and between parents and children and part of this correlation can be attributed to genetic factors. Pickering noted a correlation coefficient of about 0.2 among BP of hypertensive propositi [1] and the relationship was similar to those of height. The Montreal adoption study [6] demonstrated correlation coefficients of 0.38 and 0.16 between biological and adoptive sibs respectively while the Victorian Family Heart Study [7] estimated correlation coefficients of 0.44 for non-twin siblings, 0.78 for monozygous twins, 0.50 for dizygous twins and 0.12 for spouse-spouse pairs. All these data indicate presence of a genetic component if the environmental influence is assumed to be similar between comparison groups. Hunt et al. [8] studied life table data for 94,292 persons and found the relative risks of developing hypertension were 4.1 in men and 5 in women aged 20-39 who had at least two first degree relatives affected by hypertension. Two additional measures that are commonly used to assess the genetic component of a trait are heritability (h^2), which is the fraction of variation in disease susceptibility due to genetic factors, and sibling recurrent risk (λs) which is the degree of elevated risk of disease for a sibling of an affected individual compared with a member of the general population. The heritability of clinic systolic BP is around 15-40% and 15-30% for clinic diastolic BP [9, 10], whereas for ambulatory night-time systolic and diastolic BP the heritabilities are 32-70% and 32-50% [9, 11-13]. It is pertinent to point out that though the heritability estimates are considerable, this does not equate to magnitude of genetic effect. This is because the denominator in the estimate of heritability comprises measurement error and variances attributable to genes, shared environment, non-shared environment and unmeasured determinants. Heritability is also a property of the population studied and low heritability estimates would suggest that genetic mapping would be difficult for that phenotype. The sibling recurrent risk of hypertension is around 1.2-1.5 [14] and taking this along with heritability and correlation estimates, the hypertension and BP can be considered a trait with relatively modest genetic effect. As noted above, minimizing measurement error by using ambulatory recordings provide higher heritability estimates and using this phenotype can maximize the genetic signal [11-13].

Population variability in hypertension susceptibility and evolutionary factors

In order to dissect the genetic factors underlying hypertension, the reductionist and complexity theories need to be integrated with evolutionary theory [15-17]. Natural selection is a source of genomic variation and genetic variants that confer a survival advantage are selected for, while those that are detrimental are selected against. This occurs only in the presence of individual variation or when variations are not selectively neutral. The monogenic diseases are examples of diseases which are under very strong negative selection primarily because they affect fitness and are less likely to be transmitted to the next generation. The monogenic Mendelian forms of hypertension thus have a low prevalence, and gene mutations responsible are highly penetrant with low frequencies and high levels of allelic heterogeneity. In contrast, susceptibility variants involved in essential hypertension are likely to have low or medium penetrance, and are probably not subject to such strong selection resulting in lower allelic heterogeneity and greater prevalence of the trait. From an evolutionary perspective, essential hypertension is a disease of civilization and may be an undesirable pleiotropic effect of a preserved genotype that may have optimized fitness in the ancient environment [18]. Differing predispositions to a trait in different populations may reflect different evolutionary selection pressures ("bottlenecks") and the fact that populations do not share the same ancestral histories. It is recognized that hypertension occurs earlier and with more severity

in people of African ancestry compared to those of European ancestry [19]. The rates of hypertension and sodium sensitivity are generally higher in individuals carrying the ancestral alleles of sodium conserving genes, which show strong latitudinal clines with the ancestral sodium-conserving alleles much more prevalent in African populations and less so in the northern regions [20-22]. It is also hypothesized that the enin-angiotensin-aldosterone (RAAS) system was initially adapted for sodium conservation with modern civilizations facing detrimental effects even with its normal state of activity and adapting by selection for lesser RAAS activity [23]. All these factors support the premise that essential hypertension has a genetic component and, similar to other common multifactorial diseases, the distribution of phenotypic effect-sizes of causative gene variants is consistent with the existence of a few genetic *loci* with large effects and numerous *loci* with small effects [24].

Common variant or rare variants

There is an ongoing debate whether common or rare variants contribute to hypertension. The common variations studied are single nucleotide polymorphisms (SNPs). Common SNPs with minor allele frequency (MAF) >1% would account for more than 90% of the genetic differences between individuals. This is the basis of the common disease/common variant hypothesis which holds that the genetic variants underlying complex traits occur with a relatively high frequency (>1%), have undergone little or no selection in earlier populations and are likely to date back to >100,000 years ago [25]. As the human population rapidly expanded from a small founder pool over a short period, there was not enough time for new alleles generated during population growth to dilute out the disease-risk alleles that were common in the founder population [26-28]. Also, an allele with no effect on reproductive fitness is expected to achieve high equilibrium frequency and this is likely to be the case for genes influencing hypertension. The other competing model for hypertension is the Common Disease Rare Variant hypothesis, with an inverse relationship between the magnitude of genetic effect and allele frequency [24, 29]. This model argues that diseases are common because of highly prevalent environmental influences, not because of common disease alleles in the population [28]. Recently support for this has come from studies of rare variants of three genes *SLC12A3*, *SLC12A1* and *KCNJ1* (major mutations of which cause Gitelman syndrome, Bartter syndrome type 1 and Bartter syndrome type 2 respectively) in the general population producing clinically significant BP reduction and protection from development of hypertension [30]. The most likely scenario would be that the allelic spectrum of the disease variants is the same as the general spectrum of all disease variants. Under this neutral model, although most susceptibility variants are rare with minor allele frequencies (MAF) <1%, SNPs with MAF >1% would account for more than 90% of the genetic differences between individuals. It is plausible that these common variants might contribute significantly to those common diseases in which susceptibility alleles might not be under intense negative selection. For the genome as a whole, it has been predicted that of the expected 10-15 million SNPs with MAF >1%, approximately half have MAF >10%. Given that the number of disease variants conferring mild to moderate risks might be large, there are likely to be hundreds of common and rare variants contributing to the familial clustering of hypertension.

Monogenic hypertension

Table I summarises the rare monogenic forms of hypertension that have contributed to our understanding of salt and water homeostasis and BP regulation. The central pathway in these disorders appears to be an increase in sodium reabsorption in the distal nephron owing to dysfunction of components of the mineralocorticoid signalling pathway [31, 32]. Hypertension with low plasma renin activity is characteristic of familial hyperaldosteronism I and II (FH-I and FH-II) which are associated with excessive aldosterone synthesis that escapes normal regulatory mechanisms, and gives rise to volume-dependent hypertension that, in turn, suppresses renin release. Liddle syndrome, Gordon's syndrome and activating mineralocorticoid receptor (*MCR*) mutation in hypertension exacerbated by pregnancy are caused by mutations in sodium and chloride transporters or mineralocorticoid receptors that mimic a state of mineralocorticoid excess leading to hypertension. Congenital adrenal hypertplasia and syndrome of apparent mineralocorticoid excess involve deficiencies of enzymes that regulate adrenal steroid synthesis and activity, resulting in a build-up of precursors with potent mineralocorticoid activity and consequent hypertension.

Polygenic hypertension

The genetics of essential hypertension has proven refractory to molecular and epidemiological genetic approaches. Linkage mapping is a method of studying genetic markers of known chromosomal location that are co-inherited with the disease in a pedigree. A number of genome wide linkage analyses for hypertension as a qualitative trait and

Table I. Monogenic forms of hypertension

Disorder	*Locus*	Age of onset	Pattern of inheritance	Aldosterone level	Serum potassium level
Familial hyperaldosteronism I – Glucocorticoid remediable aldosteronism (FH I, GRA)	CYP11B1 CYP11B2	Second or third decade	Autosomal dominant	High	Decreased in 50% of cases; marked decrease with thiazides
Familial hyperaldosteronism II (FH II)	7p22	Middle	Autosomal dominant	High	Low to normal
Congenital adrenal hyperplasia (CAH)	CYP11B1 CYP17	Cchildhood	Autosomal recessive	Low	Low to normal
Hypertension exacerbated by pregnancy	mineralocorticoid receptor – MCR	Second or third decade	Unknown	Low	Low to normal
Apparent mineralocorticoid excess (AME)	11-hydroxysteroid dehydrogenase-2	Childhood	Autosomal recessive	Low	Low to normal
Liddle syndrome	ENaC β, ENaC γ	Third decade	Autosomal dominant	Low	Low to normal
Gordon's syndrome	WNK1 WNK4	Second or third decade	Autosomal dominant	Low	High

quantitative BP levels show linkage evidence to regions in almost all chromosomes. This suggests that *loci* underlying susceptibility to hypertension have at best a modest effect in the populations from which these study samples have been selected [3, 14, 33, 34] with no single genomic region having a uniformly large effect on predisposition to hypertension [35]. The inconsistency of the results between different genome scans and lack of replicability can be attributed to population and phenotypic factors – (1) different ethnic origins of the populations, (2) small sample sizes, (3) lack of stratification by gender and age and (4) limited assessment of phenotype and genetic factors – existence of multiple pleiotropic variants of low penetrance, epistasis.

Candidate gene studies

In parallel with genome wide linkage studies several groups pursued candidate gene association studies, which are hypothesis driven as genes studied are selected based on an *a priori* understanding of the roles of the encoded proteins in BP regulation. However, this strategy has not been very successful and has been plagued by lack of reproducibility. The most widely studied candidate genes are angiotensiongen (*AGT*) and angiotensin converting exyme (*ACE*). In a study of more than 10,000 individuals, –6AA, 174TT, or 235TT in the angiotensinogen gene showed increased plasma angiotensinogen levels and moderately increased risk of elevated BP (women only), but no association with BP examined as a continuous variable and no association with risk of ischemic heart disease and ischemic cerebrovascular disease [36]. The pivotal role of ACE in the renin angiotensin pathway and the demonstrated efficacy of ACE inhibitors in the treatment of hypertension has resulted in the *ACE* gene being the most studied with respect to hypertension. Plasma levels of ACE are under very strong genetic control with about 70% of the total variability being determined by genes [37]. However, studies in humans which have looked for association between polymorphisms associated with plasma ACE activity and hypertension have been mainly negative with no evidence of any association between plasma ACE levels and BP [38]. Salt-sensitive hypertension is a trait defined by BP response to salt, which has been extensively studied with candidate gene association studies. Most of the regulation of Na^+ transport occurs through ENaC and Na^+/K^+-ATPase and evidence for the involvement of these pathways comes from Mendelian hypertension and rat studies. The majority of mutations identified in Mendelian forms of hypertension-related syndromes were found in genes involved in electrolyte transport functions, including *SCNN1A*, *SCNN1B*, and

SCNN1G which encode ENaC subunits [39-41]. Also the majority of the genes from the pathways presumed to be involved in salt-sensitivity have been mapped to BP quantitative trait *loci* [3, 15, 42, 43]. *ATP1B1*, which encodes a β subunit of Na^+/K^+-ATPase, is located in a BP quantitative trait *locus* for human, rat, and mouse, and variants in this gene are associated with differences in BP levels [44]. Adducin is a heterodimeric cytoskeleton protein present in kidney and brain, and the adducin 1 gene (*ADD1*) has been found to be significantly associated with salt-sensitive hypertension in several independent studies [45]. Four SNPs in the chlorine channel gene (*CLCNKA*) have been associated with the pressor response to an acute Na^+ load [46]. There are several limitations to candidate gene approach including an inappropriate choice of candidate genes, events that take place either upstream of the points of action of the selected candidates or in the downstream signalling pathways are not tested, and the discovery of genetic variants in previously unknown pathways is precluded. Moreover it is frequently observed that underpowered follow-up studies may lead to a false-negative replication result and heterogeneity in genetic or environmental background might be another serious problem. As with linkage studies, the only true evidence of a successful association is replication in independent populations and for candidate genes in hypertension. Unfortunately, this is lacking for the majority of candidate gene association studies of hypertension.

Genome wide association studies

Genome wide association studies (GWAS) are large scale association mapping efforts using SNPs and making no assumptions of the genomic location or function of the causal variant. They provide a comprehensive approach to testing the hypothesis that common alleles contribute to heritable phenotype variation [47] and this approach has been the subject of recent reviews [47-49].

Gene-environment interaction

There is growing recognition that environmental and behavioural changes, in interaction with a genetic predisposition, have produced most of the recent increases in chronic diseases including essential hypertension [50, 51]. However, the most important implication of gene-environment interactions is that they can suggest approaches for modifying the effects of deleterious genes by avoiding environmental exposure [51]. Despite much information on both genetic and environmental risk factors, there are relatively few robust gene-environment interaction studies [52-54].

Intermediate phenotypes and pharmacogenomics

The study of intermediate phenotypes in hypertension is attractive because such phenotypes may be under a greater degree of genetic control than the final phenotype and thus studies of a moderate size may suffice to detect genetic effects. Additionally, an intermediate phenotype may enable classification into more genetically tractable subphenotypes. Intermediate phenotypes such as endothelial function and vascular stiffness may help to understand the physiological link between gene variants and established disease. Identifying the genetic predictors of the therapeutic response to drugs is the role of pharmacogenomics. The heritability basis of antihypertensive drug response is supported by the following observations. The existence of Mendelian forms of hypertension, genetic differences in drug metabolism (cytochrome P-450) or in drug receptors (β1-adrenergic receptors) and receptor response pathways (G-protein β3 subunit). In the British Genetics of Hypertension (BRIGHT) study population, hypertensive sib-pairs who were non-responsive to ACE inhibitors, ARBs or β-blockers showed significant linkage on chromosome 2p (LOD =4.84 at 90.68 Kosambi cM) [33]. This susceptibility *locus* co-localises to a region found in African-American hypertensives in the Family Blood Pressure Program, who showed evidence of linkage with hypertension status at 93 cM with a LOD score of 2.84 [55]. Thus the chromosomal 2p *locus* independently identified in different populations may contain a gene or genes for the salt-sensitive form of hypertension, which is common among Africans, and the same mechanism may be operative in a subset of white European hypertensives identified by unresponsiveness to β-blockers and ACE inhibitors. This is the first identification of a chromosomal region that is potentially a pharamcogenetic *locus*, which could identify individuals who are unresponsive to β-blockers and ACE inhibitors. Although polymorphisms in several genes have been inconsistently with the BP response to diuretics, β-blockers and ACE-inhibitors [56-61], there is robust evidence in terms of successfully using the GWAS strategy to identify genetic markers of drug adverse effects [62]. It is very likely in the future this strategy has the potential to produce clinically translatable discoveries.

Current status

Rare monogenic forms of hypertension or hypotension have all been associated with genes involved in the renal tubular electrolyte transport functions [6, 63]. These early successes were considered a portent of rapid identification of the

genes for the common essential hypertension. The fact that the genes for the rare forms of hypertension were involved in some way with renal salt handling tied in perfectly with the long favoured view of scientific reductionism in which the world is composed of nested, deterministic systems that one can analyze in a step-wise fashion. Though the common form of hypertension has a complex multifactorial etiology, the clustering of renal salt handling genes in the monogenic forms of hypertension led to the belief that other genes/pathways could be similarly dissected and one could understand the whole by examining its parts. The whole exercise in candidate gene association studies stems from this assumption. The key fact underpinning this strategy is that though hypertension involves multiple pathways, the total number of components are small and there are very few interactions between the components, thus making it a "simple system". So if one knows the inputs acting on the system and the environmental influences are minor, the result can usually be predicted [64]. But in reality, BP regulation like other physiological process is a "complex nonlinear system" with interactions between all components, and in this case to understand the behaviour of the parts one must understand the behaviour of the whole. In essence, knowing a solution to a two body problem (simple system) does not make it possible to solve a three body problem by piecing together solutions of several two-body problems. A key feature of complex systems [64] is the sensitivity to initial conditions making the BP phenotype exhibit plasticity based on the historical context of the gene and phenotypic characterisation based on single point or longitudinal measures, making replication of experimental findings problematic. The spectacular successes in identifying genes for monogenic hypertension and the equally dramatic failures with the candidate gene approach exemplifies some of the limitations of reductionism which does not work well outside defined narrow limits.

In conlusion, it is now appreciated that genetic studies of hypertension must be rigorous about the standardisation, precision and accuracy of phenotyping, quality control analysis and interpretation. The challenge is to translate the small effect size into clinically useful diagnostic or therapeutic tools with an impact on public health. There is also growing evidence for heritable changes in gene function without changes in DNA sequence (epigenetics) and structural variations, specifically sub-microscopic rearrangements between 500 bp and 5 Mb in size, commonly called copy number variation (CNV). Identification of these validated gene variants should help understand disease biology, but their relevance to clinical practice and public health will depend on whether they can improve diagnosis, prevention or treatment strategies. All this will need more efficient epidemiologic studies enrolling prospective population cohorts with informed consent along with collection and storage of biological samples, active collaboration between basic scientists and clinicians, development of novel computational and statistical approaches and incorporating large-scale genomic, proteomic, metabolomic and epigenetic analyses in a systems biology framework.

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