

The Genetic Basis of Hypertension

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ABSTRACT

Hypertension (HTN) is one of the major risk factors for almost all cardiovascular diseases including coronary artery disease, stroke, heart failure and renal failure. Nonetheless, blood pressure (BP) regulation is insufficient due to its multifactorial nature involving interactions among genetic, environmental, mechanistic and neuroendocrine factors. Essential hypertension is the most frequent diagnosis indicating that a monocausal etiology has not been identified. The identification of causal genetic determinants has been unfulfilling. Analyses of rare monogenic syndromes of HTN focusing on renal sodium handling and steroid hormone metabolism have proved the well-defined genetic frame of hypertension though they do not affect the normal distribution of BP in the general population. Genome-wide association studies (GWAS) have revealed genetic variants that are associated with BP with small effect size which cumulatively explain to a very small extent the variability of BP. New large-scale studies in the genomic arena will clarify the polygenic determinants of BP and open a perspective on translation of the progression in BP genetics to clinical use.

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Arterial hypertension as a compounding burden of public health

Hypertension (HTN), i.e. increase in blood pressure (BP) >140/90mmHg is a major risk factor for many manifestations of cardiovascular disease continuum, such as stroke, myocardial infarction, kidney failure and heart failure [1]. Cardiovascular disease is the leading cause of death worldwide, accounting for 17 million deaths. The complications of HTN are responsible for 9 of the 17 million deaths [2]. The incidence of hypertension increases with age, so >2/3 of people over the age of 75 are hypertensive. In a large European survey focusing on primary prevention, BP is regulated in only 38% of hypertensive people receiving medication [3]. This is of interest, as antihypertensive treatment has shown in many studies to be beneficial in reducing cardiovascular morbidity and mortality [4].

Causes of suboptimal BP control

The role of the interaction of mechanistic – environmental – genetic factors

There are several reasons for the insufficient regulation of BP in high-risk patients. One of the most important is that the pathogenesis of hypertension is multifactorial since environmental, mechanistic and genetic factors that remain largely unclear are involved in its etiology.

From a mechanistic hydrodynamic point of view, BP is expressed by Ohm's law: Pressure = Flow x Resistance

The flow depends on the cardiac output (L/min) and the resistance from the peripheral resistances, i.e. the tone of the arterioles and precapillary sphincters. However, the flow depends on

environmental factors (e.g. excessive salt intake) and the tone of the vessels depends on the interaction of the autonomic nervous system and the action of hormones [5]. Many other factors, such as age, obesity, smoking, alcohol consumption and physical activity, affect BP levels and make it very difficult to calculate the weight of each factor in BP regulation. Recently, genome testing has begun to be used to detect specific genotypes that underlie the “essential hypertension” phenotype [6].

Pickering, as early as 1965 supported the multifactorial nature of the genetic inheritance of hypertension and attributed particular power to the influence of environmental parameters [7]. Arterial hypertension has a moderate hereditary predisposition (30-50%) and a multitude of genes contribute to the development of essential hypertension with a small effect size (effect on arterial hypertension by 1mmHg with regard to its systolic component) [8].

In contrast, several severe hypertension syndromes that produce a large effect size (effect on blood pressure by 10 mmHg with regard to its systolic component) follow Mendelian inheritance; these syndromes are extremely rare and therefore do not significantly affect the normal distribution of BP in the general population [9,10].

The impetus for studies on the effect of genetic causes on the pathogenesis of hypertension was initially based on studies of families that examined the prevalence and inheritance of hypertension in biological children versus adopted children and in series of monozygotic and non-monozygotic twins. When a person has a first-degree affinity with a hypertensive patient then they are twice as likely as the general population to develop hypertension. As the number of first-degree hypertensive relatives increases, the risk of developing hypertension increases respectively. Further

support for the involvement of genes in the development of hypertension comes from experimental models. In animal models (rodents) with hypertension, where environmental factors can be normalized, it has become possible to identify chromosomal areas (blood pressure quantitative trait loci – BP – QTLs) that may be important for the development of hypertension [11].

Mendelian forms of hypertension

There are at least eight forms of monogenic hypertension with a clear Mendelian inheritance pattern. The contribution of these genotypes to BP variability in the general population is estimated to be very small. Nevertheless, studies of these rare forms of hypertension have shed significant light on the pathogenesis of hypertension, which is mainly related to the control of potassium (K⁺) and sodium (Na⁺) ions by the kidney as well as steroid hormones, and have provided evidence for the successful adaptation of antihypertensive therapy based on genetic testing [12]. Patients with monogenic hypertension develop hypertension early and usually the effect size is large, especially for systolic blood pressure >10mmHg. These patients cannot be considered to have essential hypertension since they have a specific genetic abnormality. Nevertheless, studies of these rare syndromes are important in understanding essential hypertension as they are the only well-defined genetic etiology in BP. Subsequently, Genome-Wide Association Studies (GWAS) will provide a further understanding of the genetic variants in the development of essential hypertension [13].

Recently, 12 genes that lead to 8 distinct Mendelian inheritance syndromes causing hypertension have been identified. Two of the 4 genes that cause Gordon syndrome have been discovered recently. Abnormal genetic polymorphisms in the genes of monogenic hypertension follow Mendelian rules of inheritance (autosomal dominant and residual types) and are phenotypically characterized by electrolyte and hormonal disorders. The serum K⁺ levels in patients with a strong hereditary history of hypertension can provide some guidance to suspect a Mendelian form of hypertension. The identification of such types of hypertension is important as in several cases it leads to the therapeutic decision (e.g. in the glucocorticoid-remediable aldosteronism, or in the treatment of Gordon syndrome with thiazides) [14].

One of the important lessons from monogenic hypertension is that the 12 genes belong to 2 main groups: 1) those that regulate Na⁺ reabsorption in the kidney and 2) those that regulate the metabolism of steroid hormones, including glucocorticoid receptors.

Glucocorticoid-remediable aldosteronism

Glucocorticoid-remediable hypertension (GRA) is an autosomal dominant disorder caused by an unequal reductive recombination between the aldosterone synthetase (CYP IIB₂) gene and the 11-β-hydroxylase (CYP IIB₁) gene. Therefore, the secretion of aldosterone synthetase is brought under the regulatory control of adrenocorticotrophic hormone (ACTH). Clinically, the phenotype varies from severe, early-onset hypertension (88%) to milder BP increase (41%) and moderate hypokalemia. Suppression of ACTH with glucocorticoids leads to a significant decrease in BP and represents the most appropriate treatment for patients with GRA [15].

Pseudoaldosteronism (Gordon syndrome)

Gordon syndrome is caused by mutations in two genes that encode serine and threonine kinases (WNK1 and WNK2). The resulting cell phenotype results from hyperactivity of the thiazide-sensitive Na-Cl cotransporter and leads to excessive Na, K, CL retention.

Clinically, Gordon syndrome manifests as hypertension, hyperkalemia despite normal glomerular filtration. Thiazide diuretics correct metabolic disorders and reduce BP in patients [16,17].

Liddle syndrome

Liddle syndrome is caused by mutations in the genes encoding the β and γ subunits of the epithelial Na channel (ENaC: Epithelia Sodium Channel). Thus, ENaCs accumulate and are continuously activated in the distal nephron. The clinical picture of the syndrome is characterized by early onset of hypertension, low aldosterone levels, hypokalemia and resistance to most classes of antihypertensive drugs. Amiloride, an ENaC antagonist, corrects the increased sodium reabsorption of mutant channels, reduces BP, and restores electrolyte disturbances [18,19].

Congenital adrenal hyperplasia

It is defined as the set of autosomal genetic disorders related to the function of enzymes for the biosynthesis of cortisol. In the classic form due to 21-hydroxylase deficiency, there is no hypertension, while we have increased blood pressure levels in 17α-hydroxylase deficiency. Coexist with salt retention and deficiency of sex hormones [20].

Apparent mineralocorticoid excess syndrome

The apparent excess of corticosteroids is an autosomal recessive disorder caused by inactivation of 11-β-hydroxysteroid dehydrogenase type II (11β-HSD2). The genetic defect leads to impaired conversion of cortisol to cortisone and to the increased bioavailability of the cortisol that activates the mineralocorticoid (MR) receptor. The phenotype is characterized by severe hypertension, hypokalaemia, and response to spironolactone [21].

Hypertension accelerated by pregnancy

A mutation in the NR3C2 mineralocorticoid receptor causes early-onset hypertension with exacerbation during pregnancy. The mutation is located in the mineralocorticoid receptor gene NR3C2. The underlying mutation was suggested to lead to constitutive MR activity [22].

Genetic determinants of essential hypertension

Essential hypertension is a complex, heterogeneous and polygenic disease. Numerous probes of the human genome provided important evidence for the existence of several chromosomal regions associated with BP. These genomic segments, known as BP-QTLs, are present in all human chromosomes, but BP-related chromosomal regions differ between series of patients of different national origins. The moderate similarity in the genetic architecture of BP-QTLs in different populations indicates that there are few common genetic variants that contribute to genetic hypertension. In the studies there is a lack of conclusive data on the correlations of hypertension and common genetic abnormalities. Also, genes with moderate pathophysiological potential are involved as responsible for the occurrence of hypertension [23].

Modern methods of genomic analysis allow the study of diversity with great resolution and push us to extend the terms of homozygosity and heterozygosity from the level of the genetic locus and allele genes to the level of unique nucleotides. Thus, today we are talking about alleles without referring to genes but to the basic unit where genetic diversity is expressed, which is based on single nucleotide polymorphisms (SNP) [24].

A SNP corresponds to a unique position on the genome that differs between individuals in the population. We then consider that this

position is polymorphic and therefore a particular individual may be homozygous or heterozygous for that position. The contribution of individual SNPs to the overall variation of arterial hypertension is expected to be moderate; however the coexistence of high-risk cumulative SNPs is expected to increase the likelihood of developing hypertension. Also, two or more SNPs that are not related to hypertension as single positions may act together leading to a large increase in BP. The term SNP refers not only to single nucleotide substitutions but also to mononucleotide insertions and deletions. The human genome contains millions of SNPs [25, 26].

Multiple gene interactions encoding components of the renin-angiotensin-aldosterone system (RAAS) and β -adrenergic signaling appear to influence the phenotype in hypertensive patients. The RAAS is central to the development of hypertension and research has long focused on the polymorphisms in the genes encoding the synthesis of RAAS proteins.

The angiotensinogen gene, which plays a very important role in the development of hypertension, is located in the small arm of chromosome 6, in the same region as the renin gene. In the Met 235 Thr polymorphism, the amino acid methionine at position 235 of the polypeptide chain has been substituted by the amino acid threonine. Ethnicity and gender affect the correlations between AGT and hypertension. Despite the significant racial differences of polymorphism by which the M235T genotypes are distributed in the populations, there is a correlation with essential hypertension in Caucasians and Japanese.

In the case of Thr 174 Met we again have a point change, namely substitution of the amino acid threonine by the amino acid methionine at position 174 of the polypeptide chain. The Thr 174 Met polymorphism was associated with BP value variation in the population and is responsible for 3.1% of the total variation in men [27-29].

Another important gene involved in the mechanism of arterial hypertension is the angiotensin-converting enzyme (ACE) gene. The ACE gene exhibits a significant polymorphism known as I/D which is determined by the insertion or deletion of a 287 base pair polynucleotide sequence located in the intron 16 of the gene [30]. One of the first publications claimed that the DD genotype was significantly more common in hypertensive patients with kidney disease and albuminuria [31]. A study in children from the USA showed that overweight children who had allele D had significantly higher systolic blood pressure compared to children with normal weight and genotype II [32].

In the Framingham study in 3095 patients, the DD and ID genotypes were found to be associated with hypertension, but only in men [33]. In conclusion, correlations between arterial hypertension and ACE polymorphisms may be affected by age, sex, other genes or environmental factors, and the results of the correlation between hypertension and ACE genetic diversity are conflicting.

Other BP regulatory genetic networks include variants that encode components of Na^+ homeostasis, intracellular signaling, and vasoactive molecules, such as NO, as well as positions encoding growth factors.

Genetic variations involved in the development of polygenic form of hypertension: focusing on a Greek patient cohort

In a genetic study of a hypertensive population where 128 Greek

families were studied, the analysis of the genetic material revealed the correlation of a region of the chromosome 17 between the genetic positions D1751814 and D175800 with the occurrence of hypertension. The genetic locus is most likely related to the N-methyltransferase (RNMT) gene located in the same region (17q21 locus).

Subsequently, a correlation was made between two polymorphisms in the region of the RNMT gene promoter (RNMT-148 and RNMT-343) in a sample of 3 nationalities: African Americans, white Americans and Greeks. These polymorphisms are associated with the development of hypertension only in African Americans. There are several reasons for the association of this polymorphism with the occurrence of hypertension only in African Americans and not in Greeks. N-methyltransferase may not play a significant role in the inheritance of hypertension in the white population or this polymorphism is not functional in whites.

Also, polymorphisms in the first exon of the NEEDD4L ligase gene of ubiquitin were detected in the above 3 populations. The polymorphisms of this gene lead to a decrease in ubiquitinylation and degradation of proteins that act as Na^+ ion pumps and thus a higher density of epithelial pumps leads to an increase in Na reabsorption and an increase in BP. In all 3 populations studied (African Americans, white Americans, Greeks) polymorphisms associated with hypertension were identified. This fact supports the hypothesis that this gene is a key genetic factor of hypertension. It was also found that the combination of 2 SNPs of CAT-844AA and CAT-262CT in the catalase gene promoter is associated with the development of idiopathic hypertension in the sample of Greek hypertensive patients, while no significant correlation was found in the African-American sample studied.

Finally, in this study it became clear that essential hypertension follows a pattern of maternal inheritance as the offspring of hypertensive mothers present a statistically significant higher risk of developing hypertension compared to the offspring of hypertensive fathers. These data are supported by mitochondrial DNA polymorphisms that contribute to the inheritance of hypertension [34].

Genetic linkage and genetic association

The success that took place during the Genomic Era has created high expectations that the correct use of Genetic Information will change the triptych: prevention-diagnosis-treatment.

In contrast to monogenic disorders, multifactorial diseases are determined by a large number of genetic and environmental (acquired) factors as well as by their interactions. Genetic linkage presupposes knowledge of genotypes between close relatives in a way that contrasts the family tree with genetic information to draw conclusions about how the various traits have been inherited. Genetic linkage has been shown to be highly effective in hypertensive families to detect monogenic hypertensive syndromes. However, it is very difficult to use the family model to detect genes associated with essential hypertension because a very large sample size is required.

However, unlike rare Mendelian diseases, combinations of different genes and their environment play an important role in the development of diseases such as arterial hypertension, diabetes mellitus and coronary artery disease. In this case of multifactorial diseases, the use of genetic linkage allows to study genetic diversity in a large number of individuals and use statistical

estimators to identify genomic regions. A large number of SNPs are collected from a large number of individuals and through statistical estimation haploblocks for the whole population are reconstituted. Haplotype bundles compose the genetic model of wider population groups. In other words, we are moving from the level of simple polymorphisms to more extended units of genetic diversity. Although each individual may carry different allele SNPs at specific locations, haploblocks are well defined, and as the haplotype defines a subset of a population rather than a specific individual, many individuals in the same population may share the same arrangement of haploblocks [35].

To investigate genetic factors that interpenetrate complex multifactorial diseases we need to perform genome-wide association studies (GWAS). In these studies that use high-performance DNA genotyping technology, millions of SNPs are genotyped across the entire genome, that is, the genome is scanned. The GWAS analysis is based on the principle of identifying common polymorphisms that are statistically different between patients - controls, where patients are considered those who express the hypertension phenotype and controls those who do not show the phenotype under study. Because the GWAS analysis determines the correlation of millions of SNPs in the genome, there is an increased likelihood of false positive correlations and results should be confirmed in large cohorts of hypertensive patients. Once the genetic association is documented, BP's response to medication should be documented [36].

Common polymorphisms: small magnitudes in the increase of systolic blood pressure \approx 1mmHg – rare polymorphisms – larger magnitudes in the increase of systolic blood pressure \approx 10 mgHg According to the theory of allele rarity, there is an overall inverse relationship between the penetrance of an allele and its frequency in the population. This is to be expected as an allele that has a large effect should in fact be rare due to the evolutionary disadvantage of its carriers in transmitting it. Very rare invasive alleles are characteristic of Mendelian monogenic diseases.

Less rare alleles with intermediate effect are in the middle, while at the right lower part of the diagram there are alleles with high frequency but low phenotypic effect (low penetrance), which are characteristic of multifactorial diseases not attributable to a single locus, but spread to a large number of genetic traits. GWAS studies with a large sample size can determine alleles with a very small degree of penetrance. The same studies show that common polymorphisms with small effect sizes and rare polymorphisms with larger sizes or even mutations may coexist [37-39].

Through GWAS approaches we can detect genotypic and phenotypic correlations for allele frequencies greater than 0.05 or, conversely, rare alleles can be detected if they have high penetrance.

In 2009, Leyy reported 4 genetic associations with systolic blood pressure (ATP 2 B1, CYP 17A1, PLEKHA7, SH2B3). The effect size was small and the systolic blood pressure variation ratio justified by 10 SNPs was 1% [40].

The largest contribution to date in terms of number of loci discovered for SBP, DBP, and HTN is by the ICBP although many other studies have contributed additional variants and also important additional information [14, 41]. The ICBP experiment of 2011 included total discovery GWAS data on 69 395 individuals and further replication genotyping in up to 133 661 subjects. The

study convincingly replicated 13 loci identified in previous, largely overlapping studies [42,43].

A total of 29 SNPs that increase the risk of hypertension were described, although with different effect sizes. For each genetic allele the effect size is 1mmHg for systolic blood pressure and 0.5 mmHg for diastolic blood pressure; even if added up, all 29 SNPs are responsible for 1-2% of the systolic and diastolic blood pressure variation.

The Case of Missing Heritability

Since hundreds of genetic polymorphisms are related to the hypertensive phenotype but explain only a small proportion (up to 2%) of the pathogenesis of hypertension and given that heritability is responsible for 30-50% of hypertension, there is a large knowledge gap in the heritability of hypertension and genetic polymorphisms cannot be used as models for the development of hypertension and future cardiovascular risk. This may be due to:

- A. There are unexplored genetic loci.
- B. The process of evolution and natural selection are expected to influence the elimination of serious and causally associated with hypertension polymorphisms in the general population.
- C. Many of the SNPs used in genotyping platforms are in interconnection imbalance with causal SNPs at varying degrees, possibly leading to an underestimation of the magnitude of the polymorphism-hypertension genetic relationship.
- D. Studies do not include in their design and analysis interactions between genes as well as interactions between genes and environmental factors, which contributes to the weak and not well-documented gene-hypertension relationship.

Conclusions

1. The study of Mendelian disorders affecting the regulation of BP at the extremes of the distribution spectrum (early and severe hypertension) identified rare etiological mutations in genes encoding proteins involved in the renal management of electrolytes as well as in the action of steroids. The importance of these mechanisms lies in the fact that these proteins are the target of antihypertensive medication (thiazides, RAAS inhibitors, mineralocorticoid receptor inhibitors). The contribution of Mendelian disorders, although they cause severe hypertension (large effect size, high penetrance) due to their rarity, is considered very small in relation to the variation of hypertension in the general population.
2. Essential hypertension is a multifactorial disease in the pathogenesis of which mechanistic, genetic and environmental factors are involved. Genetic and environmental interactions contribute to significant variation in BP between individuals. 30-50% of the arterial hypertension variation is considered to be genetically determined.
3. In recent years, genetic studies of essential hypertension have focused on analyses correlating the development of hypertension with specific gene positions by examining the whole genome (GWAS). These studies have led to the identification of abnormal loci and abnormal alleles with small to moderate effect size (low penetrance) \approx 1mmHg in the increase of systolic blood pressure and explain to a very small extent the variability of hypertension.
4. Future studies will clarify the polygenic determinants at a more practical and essential clinical level, i.e. in the pharmacological response of hypertension to various pharmacological agents, and will determine the pharmacogenomics of hypertension. Probably the causes of resistant hypertension in pharmaceutical agents will be sought there and a solution adapted to the

individualized pharmacogenomic profile will be proposed.

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