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Review Article

The role of genetics in hypertension

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ABSTRACT

In patients with primary hypertension, elevated blood pressure (BP) is considered to be a consequence of multiple factors. The 2 major factors involved are environmental factors and genes. A steady progress has been made from experimental animal studies to human genetic studies. Except for the rare monogenic hypertensive diseases, the association of genes and BP are yet to be confirmed, and the quest for "the blood pressure gene" continues. This review briefly discusses the role of genetics in HTN.

1. Introduction

Ever since Gregor Mendel studied the role of genetics in peas, role of genetics in human diseases including hypertension (HTN) have been intensely sought for. Nearly 33% of the adults suffer from HTN. Worldwide, 13.5 million deaths are due to HTN. 70%–80% of all the patients with essential HTN have a positive family history. In his publication in the lancet in 1959, Pickering GW proposed hypertension to be polygenic. In these patients, the HTN is thought to be an outcome of interaction between environmental factors and genes. Many studies have estimated that genetic factors are responsible for the variation in the HTN and its response to the therapy in about 30% of the patients.[1] The present review briefly discusses the role of genetics in HTN.

2. Nature of a complex genetic disease

There exists a continuous variation between the frequency at which a genetic variant appears and the effect it causes. It can be seen in all possible combinations. The most common combinations are a common variant causing a small effect and a rare variant causing a big effect. The latter combination is the reason behind the monogenic hypertension syndromes. Diseases that are suspected due to complex inheritance are explained by the common disease common variant theory. It hypothesizes that, allelic variants which occur at more than 5% frequency have a small individual impact and causes common diseases.[2,3]

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3. Animal studies

Animal studies conducted by George R. Meneely and Lewis K. Dahl have been seminal in understanding the role of genetics and environment in HTN. Initially they found that only 3/4th of the rats fed with high salt diet developed HTN and the remaining still were normotensive. This prompted Dahl to think on possible role of genetics in causing HTN. He interbred these strains for 3 successive generations to produce the renowned salt sensitive S rats and salt resistant R strains.[4,5] Majority of the genetic studies have been done in rats. There are 16 regions in the genome of S rat, identified by mapping studies and linkage analysis. Though all these regions are searched for "BP genes", 11β-hydroxylase is the only gene that has been identified. This enzyme is required for synthesis of aldosterone, which has a significant role in salt retention. HTN of S rats is due to an allele of this gene. Though, many animal models of HTN and its associated metabolic disturbance exist, majority of the studies use Dahl salt sensitive rat and spontaneously hypertensive rats.[6] Other models that are used in genetic studies on HTN are transgenic and knockout mouse models of the renin–angiotensin system, the Dahl/Rapp strains, NO synthase model and the bxh/hxb recombinant strains.[7]

4. Epigenetic phenomenon

The study of changes in gene expression, the cellular phenotype which is due to mechanisms not solely related to underlying genetic changes is called as epigenetics.

Initially cancer related abnormalities were blamed on epigenetic phenomena, however many diseases including HTN are related to epigenetics. After studying the HTN in people who were small at birth, Brenner and Chertow had hypothesized that HTN in these patients is secondary to reduced nephron number in the kidneys.

5. Quantitative trait loci (QTL)

Many researchers realized not all diseases which are supposed to be genetic, follow the Mendelian laws of genetics. It was proposed that, for these diseases, there exist multiple causative genes which interact with each other. However, individually these genes do not express as autosomal dominant or recessive. But these set of genes with complex interaction cause disease and they are referred to as quantitative traits loci. However, finding the QTL and their associated diseases is a challenging task ahead of medical genetics. After the identification of renal damage QTL's in rats, search for similar QTL's in humans ended upon few loci on chromosome no 1, 2, 3, 17 and 18. Further experiments, as quoted below, on these loci and for loci on any other chromosomes are being done, but no cause-association is established.

Bell et al did a two-dimensional genome-scan by taking study population from the British Genetics of Hypertension study. It consisted of 2076 affected sibling pairs and 66 affected half sibling pairs. They concluded that QTL's on chromosomes 5, 9, 11, 15, 16 and 19 have a significant impact on HTN.[8] Non-parametric linkage analysis among the cohorts of British Genetics of Hypertension study showed that chromosome 2p contains a gene that may have a role in salt sensitive form of HTN and its response to drugs.

6. Methods to study candidate genes in any disease

1. Gene expression array: To profile gene expression. It does not require a hypothesis. But interpretation is often difficult.
2. Linkage analysis: To identify a gene or genetic region that has a large effect on phenotype. If a rare familiarly inherited gene is suspected, this is the best method.
3. Association analysis: is done to associate the disease and its putative genetic variant and to identify common susceptibility variants underlying any disease.
4. Genome-wide association study (GWAS): Best usage for to identify genetic factors that influence common, complex diseases. However, requires large number of participants. Although, linkage analysis and candidate genes have given many clues on blood pressure homeostasis, not much evidence on BP QTL have been provided by them. To identify QTL more specifically, a GWAS is needed. In these studies, many genetic variants that occur commonly are screened for association with any traits. Most GWAS focus on single nucleotide polymorphisms (SNPs) and major diseases.

GWAS attempts to detect the spectrum of genetic diseases due to allelic variants and a small individual effect size. To reach the genome wide significance, a threshold of 5×10^{-8} needs to be reached and this requires nearly >1000 people need to be screened. This massive number of participants is the hurdle for performing GWAS. GWAS are also difficult to analyze because of multiple genetic variants tested. The HYPERGENES Project was a 2 staged case controlled study by Salvi et al. An ethnically diverse population was screened. It was done in 2 phases, a discovery phase and a confirmatory phase. The phase one consisted of 1865 cases and 1750 controls. Genotyping was done with 1 M illumina array. It concluded that significant association exists between HTN and rs3918226 located on eNOS gene in its promoter region. In the confirmatory phase, Meta analysis in silico data of 21714 subjects confirmed this result.[9] Newton et al did a GWAS and identified eight loci associated with HTN. The loci identified were CYP17A1, CYP1A2, FGF5, SH2B3, MTHFR, c10orf107, ZNF652 and PLCD3.[10]

Padmanabhan et al conducted a GWAS. The study population consisted of nearly 1600 HTN patients and 1700 controls. An extreme case control study was designed for follow-up validation. A locus on chromosome 16, rs13333226, in the uromodulin region 59 was identified to have significant association with HTN. Lower risk of HTN was associated with the minor G allele. Good renal function was seen in patients with decreased excretion of uromodulin.[11]

CHARGE (Cohorts for Heart and Aging Research in Genome Epidemiology) Consortium was one of the major GWAS in