REVIEW ARTICLE

Molecular basis of human essential hypertension

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Abstract

Essential hypertension (HTN) affects over one billion people worldwide. It is a complex, multifactorial, quantitative trait under polygenic control resulting from inheritance of a number of susceptibility genes and involves multiple environmental determinants in different combinations in different individuals. The completion of the draft sequence of human genome and recent advances in the genetics have resulted in identification and characterization of various genetic mechanisms that associate increased blood pressure and cardiovascular risk factors. The possible molecular mechanisms involved in homeostasis, ranging from locally acting vasoactive peptides to components of rennin angiotensin aldosterone system to epithelial sodium channels and sodium chloride transporters have been discussed. Several vasoregulatory systems including sympathetic vasoregulation and cytokines release have been studied extensively. Despite all these efforts of identification of numerous candidate genes in different ethnic populations using different approaches and technologies, the results are still inconsistent and the genetic and molecular basis of HTN remains unclear.

In view of rapid availability of useful data on various aspects of Physiology and genetics of HTN, it is pertinent to review such information focusing on association of well known candidate genes with various facets of HTN and their physiological regulatory processes. Thus HTN related risk factors, known to have interactions with genes are highlighted in this article.

Key words: genome, locus, hypertension, candidate genes

Introduction

Hypertension (HTN) is defined as a systolic blood pressure (BP) of 140 mmHg or higher or a diastolic BP of 90 mmHg or higher at the age of 20 years, and 160/95 mmHg at the age of 50 years[1]; however the Joint National Committee of World Health Organization on prevention, detection, evaluation and treatment of high BP have defined two stages of HTN in its 7th report. Stage 1 comprises systolic BP between 140-159 mmHg and diastolic BP between 90-99 mmHg; whereas stage-II with systolic BP >160 mmHg and diastolic>100 mmHg [2]. In majority of cases, a specific underlying cause of HTN is not found and they are said to have essential HTN. Essential HTN is one of the major public health problems in many countries due to its high prevalence and its association with coronary heart disease (CHD), stroke, renal disease, peripheral vascular disease and other disorders. [3]

HTN affects 28% of adult population in North America, 40% in Western countries, 25% in far East region, 15% in SAARC countries and 26% in EMRO region [4]; the prevalence and severity varies markedly with age and some estimates suggest that as many as 90% of adults will suffer from systolic HTN by the age of 80[5]. In Pakistan there are 12.5 million diagnosed cases of HTN and 12,000 die every year because of complications of this disease.

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Risk factors

HTN is a multi-factorial disorder, which results from the inheritance of a number of susceptibility genes and involves multiple environmental determinants. Existing evidences suggest that the genetic contribution to BP variation is about 30-50% [6]. Although a number of candidate genes have been studied in different ethnic populations, results from genetic analyses are still inconsistent and specific causes of HTN remains unclear. The genetic basis of HTN is complex, and the examination of functional consequences of genetic variations in particular is still challenging.[7]

Molecular and genetic medicine has challenged the supremacy of the physiological approach that has dramatically contributed to the unprecedented progress that clinical medicine has seen during the second half of the 19th and throughout the 20th century. Elaborated knowledge of physiology of sympathetic nervous system, kidney, renin angiotensin system (RAAS) etc, led to a progressive understanding of the mechanism of HTN and to the development of an array of effective BP lowering drugs making HTN a controllable disease.[8]

Many familial studies have demonstrated that about 30% of BP variance is considered to be genetically determined. Data from animal models and human population studies suggest that inherited genetic factors influence 50% of variation in BP level and that different genes affect at different ages. A few twin studies and segregation analyses have documented 30-50% variation of BP as heritable, suggesting multiple genes are involved in susceptibility to HTN, with modulation of their effects by gene-gene and gene-environmental interactions emphasizing the role of environmental factors in initiating or perpetuating the progress of HTN in humans. [9] The environmental factors seem to act only in genetically susceptible

persons. Genomic analyses for HTN even in relation to lifestyle have also been reported.[10]

Essential HTN is of unknown etiology but it is a complex interplay of genetic, environmental and other factors such as lifestyle variables, obesity, dietary salt intake, smoking, alcohol consumption and physical inactivity.[11, 12]

Molecular and genetic aspects of human HTN

Mendalian HTN (single gene)

A number of methods have been successfully used to identify mutations that cause Mendalian traits including some rare, inherited forms of HTN for which single genes are known to be involved e.g. Liddle's syndrome. Studies on Mendalian HTN has provided better understanding of etiological mechanisms including synthesis and degradation of mineralocorticoids and their receptors, sodium channel resorptive mechanisms and regulation of thiazide-sensitive sodium chloride co-transporter.[13]

Renal sodium handling is an essential physiological function for body fluid maintenance and BP regulation. Kidney specific sodium transporters in the renal tubule have been identified. Genes that regulate RAAS play a role in all aspects of BP control including radius of blood vessels and sodium and water balance. In this connection, genetic studies in general Japanese population suggested the importance of Mendalian HTN genes in genetic investigation of essential HTN.[14]

Increased peripheral resistance primarily due to changes in vascular structures and function is the major fundamental, hemodynamic abnormality. Multiple interacting humoral and mechanical factors as well as oxidative stress stimulate complex signaling pathways, which modulate vascular smooth muscle cell contraction and growth. Under normal physiological conditions, these finely tuned regulated processes maintain cell wall integrity and prevent pathological increase in BP. However under abnormal conditions increased humoral and mechanical signaling results in vascular wall thickening and increased vascular tone, which play an important role in pathogenesis and maintenance of HTN.[15]

The investigations of Mendalian disorders have identified more than 100 candidate genes in different ethnic population which provide evidence of linkage with HTN. However these genetic analyses are mostly inconsistent and have small contribution in some rare forms of HTN. Glucocorticoid remediable aldosteronism, apparent mineralocoricoid excess and mutation in the mineralocorticoid receptor gene have brought useful information about minearlocorticoid-induced HTN.[16]

Multiple gene screening for HTN

Two largest genome scans for BP i.e. Family Blood Pressure Program (FBPP) and the British Genetics of Hypertension Study (BRIGHT) have identified new loci having significant linkages in almost every chromosome; whereas association studies have implicated more than 66 genes, but virtually all failed to show consistent replication in other settings.[17]

From the analysis of data on the genetic basis of BP control, it appears that several dozen genes with modest individual effects are intervening in the regulation of BP. Most of these genes encode proteins that either mediate or are involved in the control of renal sodium handling. Several genes encoding proteins that exert a direct or indirect effect on sodium homeostasis have been located in more convincing loci (1q, 2p, 2q, 4q, 6q, 12q, 17q).[14] The sensitivity of an individual will depend on the functional interactions between these genes and on interactions with several environmental factors. A genome wide scan performed in Scandinavian sib-pairs identified HTN susceptibility loci on chromosome 14, and 2.[18] Another study identified 54 markers as potential HTN susceptibility loci by three-steps screening of three independent case-control populations. A study on adult nuclear families that included monozygotic and dizygotic twins showed that genetic and shared environmental components accounted for 64% and 31% of total variance in systolic BP respectively.[14]

Hypertension Genetic Epidemiology Network have indicated regions for BP traits together with several coincident regions for phenotypically correlated traits including systolic BP response to a postural challenge and body mass index. Thus HTN susceptibility arises from the actions of multiple genome sequence variations.[19]

Meta analysis of genome-wide scan for BP

Follow up studies in African-American and Nigerian samples involving positional cloning efforts of the combined families showing linkage evidence in 2p regions need verification for precise identification.[20] A study on a Chinese population failed to find any support for a significant contribution of five candidate genes (lipoprotein lipase, leptin, leptin receptor, alpha adducin & beta-3 adrenergic receptor) to the pathogenesis of essential HTN.[21]

The human renin is an attractive candidate for involvement in the underlying cause of HTN; thus a study in Japanese population suggested that the mis-sense mutation in exon 9 may affect the enzymatic function of renin and consequently may be involved in etiology of HTN. [22] Genome scan among Nigerians found linkage signals for systolic BP on 19p & 19q and for diastolic BP on 2p, 3p, 7p, 7q and 10q; however

accumulated data may indicate in particular 2p, 3p and 19p. Genome scans reported significant candidate genes on chromosome 14 and 2 and 12. [23]
When main findings of all human genome scans were summarized, it was observed that all human chromosomes except 13 and 20 have BP, HTN or pre-eclampsia loci. Chromosomes 1, 2, 8, 11, 12, 15, 16, 18, and 19 have regions that have been found in more than one study yielding some consistent encouraging support for BP loci.[24]

Future Perspective

There are great expectations for the future with regards to advancements in transcriptomics, proteomics and application of physiogenomic and newly emerging epigenomic approaches to hypertension research, that promises to provide deeper insight into genetics and physiology of BP regulation and hence hypertension.

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