Gene polymorphism and hypertension

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Abstract

Hypertension is a significant health problem worldwide and affects more than 20% of the adult population. This disorder has an important role in morbidity and mortality of heart and kidney disease patients. It is believed that essential hypertension is a multifactorial and polygenic disease; resulting from an interplay between environmental and genetic factors. In this paper, we will review studies that have inspected new genome screen and introduced a new viewpoint on candidate genes of essential hypertension. We discuss on polymorphism of candidate genes which related in the pathogenesis of hypertension and take from experimental models or knowledge of the pathophysiology. Study on genetic factors of hypertension may be developing new treatment for these patients.

Keywords: Essential Hypertension, Cardiovascular Disease, Gene, Candidate Gene, Polymorphism

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Introduction

Hypertension (systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg) is a significant worldwide health problem, because it affects more than 20% of the adult population. Nearly 25% of Iranians (aged 25-64 years) have hypertension and 46% (aged 25-64 years) have prehypertension.[1] This disorder has an important role in the morbidity and mortality of heart and kidney disease patients.

Hypertension without any identifiable cause is called essential hypertension (EH), and comprises 95% of all cases. The other type of hypertension is called secondary hypertension (monogenic or mendelian forms), affecting only 5% of hypertensive patients, including aldosteronism, Liddle's syndrome, and Gordon's syndrome patients**.** These disorders are caused by single gene mutation, are unusual, and display early and sever hypertension. Monogenic forms are transmitted in a mendelian manner and comprise at least nine nuclear and one mitochondrial genes.[2]

It is believed that EH is a multifactorial and polygenic disease; it results from an interplay between environmental (such as diet rich in sodium, obesity, alcohol, smoking, and stress), and genetic factors. Experiments on animal models indicated that ten or more polygenes participated in management of blood pressure.[3] It is not clear how many genes impact blood pressure, but alleles at various loci are proposed to affect the outcome of the disease.

This short review mainly depicts studies that have studied new genome screen types and introduced new viewpoints on candidate genes of EH.

Candidate genes access

Candidate genes are selected because of their role in the pathogenesis of hypertension.

New candidate Genes

1-Glutathione S-transferases (GSTs)

GSTs play an important role in defense against oxidative stress.[4] Much evidence has indicated that oxidative stress is involved in pathogenesis of hypertension.[5] GSTs are polymorphic super gene family, and in this family GST M1 (chromosome1p13.3), GST T1 (22q11.23), GST A1 (6p12.1) are further studied and compared to other genes.[6] Identifying GST A_1B allele is known as a genetic risk factor for hypertension.[7] Bessa et al. also reported that GST M1–ve/GST T1-ve was a possible genetic factor to augur the development of EH.[8] Homozygous deletion of the GST gene (null genotype) causes reduction in enzyme activity. In Italian patients the association between $GSTT_1$ null phenotype, and EH in the general population and in woman were approved. In addition, GSTT1 is considered as a sex–specific candidate gene for EH.[9]

2-Urotensin II (UTS_2)

UTS_2 is a cyclic peptide which plays a role in vasoconstriction, and induces potent changes in vascular tone regulation. UTS_2 generated reactive

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oxygen species (ROS) by activation of nicotinamide adenine dinucleotide phosphate oxidase in human vascular smooth muscle cells. UTS_2 and its receptor are expressed in the cardiovascular system.[10] Plasma level of UTS_2 is elevated in EH subjects. S89N single-nucleotide polymorphism of the UTS II has also showed to have association with hypertension (in north-western China and Hong-Kong Chinese).[11]

3-Neural precursor cell expressed, developmentally down-regulated 4- ligase (NEDD4L)

NEDD4L, E_3 ubiquitin protein ligase, (18q21) is involved in the ubiquitination of Several target substrates and has a critical role in epithelial sodium transport by regulating the cell surface expression of the epithelial sodium channel (ENaC); this protein decreases the number of ENaC present on the plasma membrane.[12] Studies have showed that NEDD4L Knockout mice have high blood pressure .[13]

It is indicated that a common SNP (rs4149601), is associated with EH in African American, and white American. However, this association was not observed in Chinese Hans, in these subjects rs3865418 polymorphism was associated with hypertension.[14] Moreover, in Kazakh females two other SNPs, 296921-296923delTTG and rs2288775, were associated with EH.[15]

4-Renal kallikreinKinin system

Bradykinin is produced from Kininogens by the Kallikreins (proteolytic enzymes). Bradykinin is involved in increased vascular permeability, vasodilation, natriuresis, and diuresis. Impaired functioning of this system may have a significant impact on the early development of hypertension. In essential hypertension urinary kallikrein activity is decreased.[16] In Chinese Han subjects, polymorphism of rs5517 (Glu162Lys) in KLK1 was significantly correlated with EH.[17]

5- E-Selectin

The evidence suggests that hypertension is associated with endothelial dysfunction. Actually endothelial dysfunction includes a specific state of endothelial cell activation, which causes increased expression of inflammatory cytokines, and adhesion molecules, and eventually leads to atherosclerotic lesion. Several molecules are involved in this process that result from multiple sources, but E-selectin (a cell surface glycoprotein) is exclusively expressed in activated endothelium.[18,19]

Plasma level of E-selectin is increased in hypertension patients.[20] Several polymorphisms of this gene are associated with EH, including A561C polymorphism,[21] C602A and T1559C polymorphism in Chinese subjects.[22] Moreover, rs5361A/C polymorphism of E-selectin is considered as a risk factor for EH among Uygur, Kazakh and Han individuals.[23]

6-Phosducin

The sympathetic nervous system has an important role in blood pressure evaluation.[24] Phosducin regulates G-protein and controls sympathetic activity in postsynaptic ganglia. This protein is more expressed in retina and pineal gland and in at a lower level in the sympathetic ganglia. Phosducin is not expressed in the heart, kidney and blood vessel. Recently a study indicated that mice with phosducin deficiency showed stress-dependent hypertension, which was the result of elevation in sympathetic tone. This study also approved that phosducin gene influences stress-dependent blood pressure and can help in the treatment of hypertension.[25] Phosducin rs12402521 polymorphism foretells obesity-related hypertension.[26]

More studied genes

1-Renin-Aniotensin-Aldosterone System (RAAS)

It is known that RAAS affects all aspects of blood pressure control, vascular tone, water homeostasis and various physiological functions (e.g. regulation of growth and proliferation, apoptosis or signal transmission).[27]

Much evidence has suggested that aldosterone, the principal human mineralocorticoid, is involved in the development of hypertension and other cardiovascular diseases.[28] Even in the physiological range, increased plasma level of aldosterone causes the development of hypertension.[29]

It is reported that T-344C and A6547G variants of aldosterone synthases are associated with EH in Anglo-Celtic females.[30] In addition, association of CYP11B2 -344C/T to aldosterone synthase and essential hypertension is confirmed in a Chinese group.[31]

One of the foremost and perhaps the most examined gene which has correlation with hypertension is angiotensinogen.[32] The association between variants in the core-promoter element1 ($AGCE_1$) of angiotensinogen gene is determined. $AGCE_1$ has an important role in regulation of angiotensinogen transcription. Studies have showed that C-18T polymorphism in $AGCE_1$ was a genetic risk factor for EH in Japanese people.[33] Moreover, it is indicated that M235T polymorphism of Angiotensinogen (AGT) has an important association with EH in white and Asian subjects.[34]

Angiotensin-converting enzyme (ACE) is another constituent of RAAS (by production of Angiotensin II), and is involved in high blood pressure.[35] The correlation between ACE gene I/D (insertion / deletion) with EH is a controversial issue. Although, some studies confirm the association between ACE gene I/D and EH in male and female subjects, some

studies rejected this association.[36-38] These result may be due to racial and environmental factors.

A study on a large number of Japanese people (n: 5014), chosen from the common population, showed that ACE gene polymorphism deletion/deletion (ACE D/D) was associated with increased risk of hypertension in men.[39]

Angiotensin II, via binding angiotensin II type I receptor (AT1R), is involved in regulation of vascular tone and blood pressure. Several polymorphisms of AT1R are reported, but A1166C polymorphism is better known.[40] The association of this polymorphism with the risk of hypertension in Iranian woman has also been reported.[41]

2-Adrenergic system

This system contributes significantly to the output of the heart, vascular tone, sodium reabsorption, and rennin release. Hence, it is a remarkable system and researchers can drive candidate genes for hypertension.

Some studies showed that sequence variations in the human α_2-adrenergic receptor genes ($ADRA_2A$ and $ADRA_2C$) are associated with hypertension in Black people,[42] but one other study showed the lack of this association.[43]

Another candidate gene of this system is B_2-adrenergic receptor ($ADR\beta_2$), which is a mediator of the vasodilator response to adrenergic agonist.[44] Several studies showed that $ADR\beta_2$ has a role in blood pressure control and the risk of hypertension.[45] Three polymorphisms of $ADR\beta_2$ gene influence the receptor function of Arg16Gly, Gln27Glu (amino acid replacement), and T-47C (a promoter variant).[45]

It has also been reported that Arg16Gly is associated with hypertension.[46] However, other studies showed no association between these polymorphisms and hypertension.[47] These different results may be due to unidentified haplotype effects, since these studies were confined to the investigation of individual nucleotide polymorphisms (SNPs).

3-G-protein interplays

G-proteins (guanine nucleotide-binding proteins) are important signal transducing molecules in cells. Signaling pathway mediated by these molecules has an important role in the development and maintenance of the hypertensive state.[48] It has been observed that G-protein signaling is increased in the cultured cells of hypertensive patients.[49]

Some studies showed that G-protein β_3-subunit gene C825T polymorphism is associated with hypertension;[50] however, some studies showed a negative association.[51] Therefore, further examination is needed to confirm these finding.

An important interaction between this polymorphism and ACE I/D for the development of EH is seen in Korean subjects.[52]

4-Endothelial nitric oxide synthase gene

Endothelial NOS (eNOS) also known as NOS3, generates nitric oxide (NO) in blood vessels from L-arginine. Nitric oxide has a key role in controlling vascular tone and blood pressure .[53]

A meta-analysis (n:11248) showed that the eNOS G894T gene polymorphism may be contributing to the increased risk of EH in the Chinese population, especially in the Han ethnicity.[54] Moreover, it has been reported that eNOS polymorphism rs891512 (G24943A) is associated with hypertension in the Chilean population.[55]

Another polymorphism of eNOS is Glu298ASP polymorphism that has a functional effect on eNOS protein and is associated with essential hypertension.[56]

Results

According to experiments and researches, genetic factors are involved in the process of hypertension including pathogenesis, diagnosis, treatment, and prevention of hypertension. Considering the importance of genetic hypertension and the diversity of the related genes, evaluation of these genes and the study of new genes are necessary. It is hoped that by deducting related genes for EH, we be better able to diagnose those at risk and develop new treatments for these patients.

Conflict of Interests

Authors have no conflict of interests.

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