The association of genetic variations with sensitivity of blood pressure to dietary salt: A narrative literature review

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Abstract
Salt sensitivity of blood pressure (BP) is an independent risk factor for cardiovascular morbidity. Up to 50% of patients with essential hypertension are salt-sensitive, as manifested by a rise in BP with salt intake. Several genetic variations have been identified as being associated with salt sensitivity. The present study aimed to review the evidence on the effect of gene polymorphisms on the salt sensitivity of BP. We searched in PubMed website from 1990 to 2011, with the use of following keywords: “hypertension, dietary salt, polymorphisms, and blood pressure”. The effect of sodium intake on BP differed by genotype at the genes of the renin-angiotensin system, aldosterone synthase, cytochrome p450 3A, epithelial sodium channel genes, genes of sympathetic nervous system, β-3 subunit of G-protein, alpha-adducin, endothelial nitric oxide synthase, Kallikrein-Kinin system. These approaches suggest that these polymorphisms may be potentially useful genetic markers of BP response to dietary salt. There is evidence that genetic predisposition modulates the BP response to diet. Therefore, diet and nutrition can mitigate or enhance the effects of genetic predisposition. Increasing our knowledge of this relationship can lead to individualized treatment and increased understanding of hypertension.

Keywords: Hypertension, Genetics, Diet Therapy

Introduction
Hypertension is a major worldwide risk factor for cardiovascular diseases (CVDs) such as heart attack, congestion, heart failure, stroke, and peripheral vascular disease.1 The prevalence of hypertension has dramatically increased in recent years.2 Essential hypertension is a complex disease that characterized by chronically elevation in blood pressure (BP) with no specific underlying medical or biological cause.3 As that shown in the previous studies in the field of similar problems such as hyperlipidemia and other CVDs,4 hypertension is a complex trait resulting from interaction of multiple genetic factors and lifestyle exposures including: dietary salt intake, alcohol consumption, and body weight.5 The heritability of hypertension is often reported in the range of 30-60%.6

Requirements and tolerable upper limits of nutrients could be different in different people.7 Several studies of nutritional genomics have shown that some of the gene variations could influence the level of nutrients requirements.8 On the other hand, intake of some nutrients could alter the gene expression and protein synthesis.9

High dietary sodium intake is the most prevalent risk factor in modern societies. Although many studies found that high dietary salt intake is associated with hypertension, but BP responses to high and low salt intake may be influenced by various genetic factors10 and some studies have suggested that dietary sodium restriction may not be beneficial to everyone. Salt restriction has been reported to decrease cognitive function in salt sensitive and salt resistant population;11 thus, there is a need to recognize the genetics determinants of salt sensitivity that increase our understanding of the mechanism underlying hypertension and finally distinguish salt sensitive from salt resistant subjects.

Salt sensitivity of BP is defined by the observed changes of arterial pressure as daily salt intake is changed.12 Most studies searching for genetics causes of essential hypertension have been observed association between candidate genes with salt sensitive hypertension. These genes including:
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renin-angiotensin converting enzyme (ACE) gene, angiotensinogen (AGT) gene, angiotensin II type 1 receptor, epithelial sodium channel (ENaC) genes, 11-beta hydroxy steroid dehydrogenase (11-BHSD) genes, sympathetic alpha receptor gene, beta receptor gene, endothelial nitric oxide synthase gene, adducin gene, and others.15

This narrative literature review outlines some of the genes associated with salt sensitive hypertension; emphases on genetic variations related to salt sensitivity in individuals and highlight the recent finding on the genetic basis of salt sensitive hypertension.

Genes of Renin-Angiotensin System (RAS)
The renin-angiotensin system (RAS) is the most important regulation of homeostatic system that controls body fluid volume, electrolyte balance, and BP.14

Components of RAS were studied as candidate genes for salt sensitive hypertension. The most studies have examined several loci within this system: the ACE gene, the AGT gene, and the angiotensin type 1 receptor gene.

ACE Gene
Many studies have examined the association between ACE and salt sensitivity.15-17 Meneton et al. found that the prevalence of salt sensitivity hypertension in II phenotype and ID phenotype is significantly higher than DD phenotype.15 Zhang et al. found that ACE I/D had been significant association with salt sensitivity hypertension.17 However, reports of the association between ACE genotype and salt sensitivity hypertension were inconsistent. Strazzullo et al. in a meta-analysis of 145 case–control studies observed that DD homozygote and ID heterozygote had increased CVD, but not for hypertension in contrast with II homozygote.18

AGT Gene
Norat et al. found that molecular variants in the AGT gene including M235T, T174M, and mutation in the promoter region that involve in the insertion of adenine instead of guanine (G-6A) had been a positive association with salt sensitivity hypertension19 that was in line with results of two previous studies.20,21 Schorr et al. found that the presence of the AA (or TT) genotype in the promoter region is associated with salt-sensitive BP.21 Also, Hunt et al. found an association between AGT-GG linkages with AGT M235T with a decrease in BP after a decrease in sodium intake.22 Beeks et al. concluded that patients who are homozygous for M allele had lower BP after mild salt restriction compare with TT and MT genotype.23 Svetkey et al. found that BP response to the dietary approaches to stop hypertension (DASH) diet is higher in the genotype of G-6A AGT SNP than GG genotype.24

Angiotensin Type 1 Receptor
Anginotensin II regulates vascular contracting, BP and sodium reabsorbing by kidney through binding with angiotensin II receptor.25 Two subtype of gene variations of angiotensin II type 1 receptor, 1A (AT1A R) and 1B (AT1B R), may effect on BP.26 Moreover, Gu et al. found an association between rs4524238 alleles G/A and A/A with salt sensitivity hypertension.27

Aldestron Synthase
Aldestron secretes by the adrenal gland and has been important in the regulation of water electrolyte balance.28 This hormone synthesize by the aldeosterone synthase enzyme, which is encoded by the CYP11B2 gene.29 Many studies reported that CYP11B2 polymorphisms, especially −344C/T are associated with salt sensitivity hypertension.30-32 However, in two studies CYP11B2 T344C polymorphism was not associated with hypertension.18,23

11ΒHSD2 Gene
Mineralocorticoid activity may be increased with decreased activity of 11BHSD2, which inactivates 11-hydroxy steroids in the kidney, thereby protecting the nonselective mineralocorticoid receptor from occupation by glucocorticoids.33 Smolenicka et al. found that Mutations in the 11BHSD2 gene may lead to a rare form of salt sensitive hypertension.34 Alikhani-Koupaei et al. identified polymorphism G534A in exon 3 of this gene could increase susceptibility to salt sensitive hypertension.35

Cytochrome p450 3A (Cyp3A)
Cytochrome p450 3A (Cyp3A) is a subfamily of cytochrome P (CYP) 450. This group of cytochromes are involved in the metabolism of drugs (e.g., anti-hypertensive drugs) and endogenous substrate such as steroids. These
metabolites effect on renal sodium transport. Components of Cyp3A subfamily are located on chromosome 7q22. These genes include Cyp3A4, Cyp3A5, Cyp3A7, and Cyp3A43 (cyt3). Cyp3A5 is of particular interest because it is expressed in the kidney; Cyp3A5*1 expresses the wild-type protein while the Cyp3A5*3 allele (A6986G, rs776746) reduces Cyp3A5 protein expression. In a Japanese population, Zhang et al. found that BP was associated with the level of salt intake in Cyp3A5*3/*3, but not CYP3A5*1/*1.

ENaC Genes

ENaC has major roles in Na⁺ reabsorption in the distal tubule, regulation of extracellular fluid volume and BP. Lifton et al. found that T594M mutation of the β-subunit in black people is associated with a greater chance of hypertension compared with individuals without this mutation.

On the other hand, neural precursor cell expressed developmentally downregulated 4-like (NEDD4L) is an ubiquitin ligease, express in the distal nephron and regulates the expression of the epithelial Na⁺ channel. Some studies reported association between variation in NEDD4L and salt sensitive hypertension. Dahlberg et al. found that a common polymorphism located in intron 2 (rs4149601, A/G) of the NEDD4L gene was found to be associated with salt sensitive hypertension.

Manunta et al. found a combination of two common single nucleotide polymorphisms (rs4149601 and rs2288774) located in the NEDD4L gene is associated with salt sensitive hypertension and suggested that carriers of NEDD4L rs4149601 G-allele have higher ENaC expression compared with carriers of A-allele.

Genes of Sympathetic Nervous System

The sympathetic nervous system is a primary regulator of acute change in BP and increased sympathetic function has reported in salt sensitive hypertension. Weber et al. found that salt-sensitive men have increased noradrenergic receptor sensitivity and circulating cortisol levels.

The genes encoding for β2-adrenergic receptor (ADRB2) is located on chromosome 10q24 and encoded 477 amino acids. Eisenach et al. found that an amino terminal variant in the β2-adreno receptor that encodes glycin instead of argenin (Arg16gly) has been associated with salt sensitive hypertension. Pojoga et al. found a Similar association between this polymorphism and BP in normotensive people. Svetkey et al. reported that dietary Na⁺ restriction blunted the increased NO-mediated β2-ADR responsiveness in Gly16 homozygotes observed in a previous study after normal dietary Na⁺ intake and demonstrated that β2-ADR downregulation might serve to explain the decreased β2-adreno receptor expression on the fibroblasts of salt sensitive individuals compare with salt resistant and normotensive people.

Another study has been found that the β2-ADR C79G and β2-ADR A46G SNPs were associated with salt sensitive hypertension. Pojoga et al. have reported that greater risk of salt sensitive hypertension is associated with an allele of A46G and the C allele of C79G. They compared the dietary change (from low- to high-sodium balance) in mean arterial pressure (MAP) among the 171 hypertensive subjects. Although baseline (low-sodium) BP was similar among genotype groups, MAP differed significantly by genotype, the 46AA and 79CC homozygotes demonstrated the greatest MAP.

β-3 Subunit of G-Protein

The β-adrenoreceptor-G-protein system is essential for function of adenylyl cyclase. Bagos et al. have been reported that polymorphism C825T in exon 19 is associated with salt sensitive hypertension. The T allele of this polymorphism is associated with higher risk of salt sensitive hypertension. Siffert et al. found that carriers of TT homozygotes and TC heterozygotes have a higher risk of hypertension compared with CC homozygotes.

Alpha-Adducin

Adducins are a cytoskeletal protein that may regulate the membrane organization of spectrin-actin. Manunta et al. found that a mutation (Gly460Trp) in human’s α-adducin was reported to be associated with salt sensitive hypertension. Manunta et al. found the association between Gly460Trp allele and hypertension in some population. Wang et al. in a recent meta-analysis involving 454 salt sensitive and 366 non-salt sensitive participants concluded that the association between ADD1 Gly460Trp and salt sensitivity is statistically significant in Asian, but not Caucasian populations; the difference may be related to the greater frequency of ADD1 Gly460Trp in Asians than in Caucasians. Wang et al. found that the interaction among ADD1 Gly460Trp, ACE DD, and CYP11B2 −344CC may contribute to the BP response to dietary salt.
Endothelial Nitric Oxide Synthase

Nitric oxide (NO) is a vasodilator that produced from l-arginine by NO synthase. Harsha et al. reported the association between Glu298Asp variant with hypertension.53 Miyaki et al. found that two polymorphisms of NO synthase, T786C and G894T have been associated with essential hypertension.54 Dengel et al. found an association between T786C polymorphism and salt sensitive hypertension.55

Kallikrein-Kinin System

This system has important roles in the kidney to increase renal blood flow.56 Chao et al. found that the Q121E SNP of kallikrein gene was reported to be associated with hypertension.55 Cervenka et al. found that deletion of the bradykininB2 receptor gene in mice produces salt-sensitive hypertension.58

Conclusion

There is evidence that genetic predisposition modulates the BP response to diet. On the other hand, diet and nutrition can mitigate or enhance the effects of genetic predisposition. Increasing our knowledge of this relationship can lead to physiologically individualized treatment and increased understanding of Pathophysiology. Major focuses in clinical research are to develop personalized treatment strategies that are preemptive and to allow persons to be proactive. While we await new studies that allow us to tailor such interventions and treatments, we must not lose sight of the wealth of information already accumulated on the effects of lifestyle modifications on BP. Reduced sodium intake, the DASH diet, weight loss, and exercise have substantial effects in almost all subgroups of the population and should continue to be widely and broadly promoted.

Conflict of Interests

Authors have no conflict of interests.

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