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Original Article

Replicated Association between *SLC4A4* Gene and Blood Pressure Traits in the Korean Population

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Recent genome-wide association studies (GWAS) have identified a number of common variants associated with blood pressure homeostasis and hypertension in population. In the previous study, single nucleotide polymorphisms (SNPs) in the *SLC4A4* gene have been reported to be associated with hypertension in Han Chinese population. We aimed to confirm whether the genetic variation of *SLC4A4* gene influence the susceptibility to blood pressure and hypertension in Korean population. We genotyped variants in or near *SLC4A4* in a population-based cohort including 7,551 unrelated Korean from Ansan and Ansung. Here, we performed association analysis to elucidate the possible relations of genetic polymorphisms in *SLC4A4* gene with blood pressure traits. By examining genotype data of a total of 7,551 subjects in the Korean Association REsource (KARE) study, we discovered the *SLC4A4* gene polymorphisms are associated with blood pressure and hypertension. The common and highest significant polymorphism was rs6846301 (β=0.839, additive P=0.032) with systolic blood pressure (SBP), rs6846301 (β=0.588, additive P=0.027) with diastolic blood pressure (DBP), and rs6846301 (OR=1.23, CI: 1.09~1.40, additive $P=1.2 \times 10^{-3}$) with hypertension. Furthermore, the SNP rs6846301 was consistently associated with both blood pressure and hypertension. Consequently, we found statistically significant SNPs in *SLC4A4* gene that are associated with both blood pressure and hypertension traits. In addition, these results suggest that the individuals with the minor alleles of the SNP in the *SLC4A4* gene may be more susceptible to the development of hypertension in the Korean population.

Key Words: Blood pressure, Hypertension, *SLC4A4*, SNP, Association

INTRODUCTION

Blood pressure (BP) is complex trait regulated by various genetic and environmental factors, and untreated high BP, or hypertension (HTN), is associated with increased mortality on public heath, and genetic polymorphism is understood to be an important factor in the development of hypertension. One of every four adults globally is hypertensive, and the number of adults with hypertension in 2025 is predicted to increase by about 60% to a total of 1.56 billion people (Kearney et al., 2005).

SLC24A4, a sodium/potassium/calcium exchanger, gene was reported as a potential candidate gene for blood pressure regulation (Adeyemo et al., 2009). Potassium-dependent sodium/calcium exchangers are thought to transport 1 intracellular calcium and 1 potassium ion in exchange for 4 extracellular sodium ions (Li et al., 2002). Rare variants in the two genes, *SLC12A3* and *SLC12A1*, which alter renal salt handing, were shown to influence BP variation in the general population (Ji et al., 2008). Given the limited functional data available on potassium dependent sodium/calcium exchangers, these genes are worth investigating further as a potential candidate gene for hypertension.

SLC25A42, (encoded by the *SLC25A42* gene), which is

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a carrier protein that transports cofactor coenzyme A and adenosine 3',5'-diphosphate into the mitochondria in exchange for intramitochondrial (deoxy) adenine nucleotides and adenosine 3',5'-diphosphate (Fiermonte et al., 2009). SNPs in this region were associated with LDL cholesterol and triglyceride levels in a whole genome analysis of European populations (Willer et al., 2008). *SLC25A42* gene was identified as a suggestive evidence of association for hypertension (Fox et al., 2011).

The human *SLC4A4* gene (solute carrier family 4, sodium bicarbonate cotransporter, member 4) is located in chromosome 4q21 region and encodes a sodium bicarbonate cotransporter (NBC) involved in the regulation of bicarbonate secretion and absorption and intracellular pH. Mutations in this gene are associated with proximal renal tubular acidosis. NBC are expressed in various nephron segments and are essential to acid-base and electrolyte homeostasis (Soleimani and Burnham, 2000).

Most studies were conducted with Caucasian and European samples, and the findings may or may not be applicable to Korean population. So we conducted replication analysis in Korean of susceptibility loci for hypertension identified recently from genome-wide association studies. Following the report that an *IGF1*, *SLC4A4*, *WWOX*, and *SFMBT1* genes polymorphism might contribute to the prevalence of hypertension in Han Chinese (Yang et al., 2012), SNPs in *SLC4A4* gene have been extensively tested as the genetic factors of blood pressure and hypertension in the Korean population.

In this study, we examined the genetic variations in *SLC4A4* gene to be associated with blood pressure levels and risk of hypertension in the Korean population. Notably, this study provides insight into the relation of *SLC4A4* gene with hypertension.

MATERIALS AND METHODS

Subjects and clinical characteristics

Subjects in the Korean population in the Korean Association REsource (KARE) study were described in more detail by other study (Cho et al., 2009; Jin et al., 2012). For quantitative blood pressure traits analysis, 961 subjects who were undergoing antihypertensive treatment were excluded and the remaining 7,551 subjects [3,747 men (49.6%); 3,804 women (50.4%)] were investigated. A case-control study was performed between hypertensive cases (n = 1,968) and normotensive controls (n = 4,452). Hypertensive cases were recruited -- base on systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg in addition to the subjects who were receiving hypertension medication, were generating a total of 1968 cases. Normotensive controls were defined as SBP < 120 mmHg and DBP < 80 mmHg. Clinical characteristics of the subjects are summarized in Table 1. This study was approved by the institutional review board of the Korean National Institute of Health (KNIH). Written informed consent was obtained from all subjects.

Measurement of blood pressure

Blood pressure measurements were taken three times in the supine position using a mercury sphygmomanometer (Baumanometer; W. A. Baum, Copiague, NY, USA) with an appropriate cuff size by trained nurses at clinics, and the average value data was used for this study. Before the first measurement, subjects rested for 5 min, and three measurements were taken at least 2 min apart.

Genotyping and selection of *SLC4A4* gene SNPs

The detailed genotyping, quality control processes and quantitative traits including SBP and DBP were described in the previous report (Cho et al., 2009; Jin et al., 2012). Briefly, most DNA samples were isolated from the peripheral blood of participants and genotyped using the Affymetrix Genome-Wide Human SNP array 5.0 (Affymetrix, Inc., Santa Clara, CA, USA). The accuracy of the genotyping was calculated by Bayesian Robust Linear Modeling using the Mahalanobis Distance (BRLMM) algorithm (Rabbee et al., 2006). Samples that had genotyping accuracies were lower than 98%, high missing genotype call rates (≥4%), high heterozygosity (>30%), or gender biases were excluded.

The SNPs that we analyzed were selected from the KARE data, based on their positions within the gene boundary (5 kb upstream and downstream of the first and last exons, respectively) (Table 2). The positions of the

Table 1. Basic characteristics of the subjects used in this study (total subjects = 8512)

Variables	Quantitative trait analysis*	Case-control analysis**	
Number of subjects	7,551	Normotensive (4,452)	Hypertensive (1,968)
Gender [men (%)/women (%)]	3,747 (49.6) / 3,804 (50.4)	2,062 (46.3) / 2,390 (53.7)	910 (46.2) / 1,058 (53.8)
Age (*M* years ± *SD*)	51.44 ± 8.78	49.39 ± 8.11	56.75 ± 8.45
Body mass index (BMI) (*M* kg/m^2 ± *SD*)	24.42 ± 3.07	24.06 ± 2.94	25.63 ± 3.27
Systolic blood pressure (SBP) (*M* mmHg ± *SD*)	115.65 ± 17.25	104.69 ± 9.15	139.42 ± 17.27
Diastolic blood pressure (DBP) (*M* mmHg ± *SD*)	74.21 ± 11.27	67.68 ± 7.72	86.97 ± 10.9
Total cholesterol (*M* mg/dl ± SD)	190.68 ± 35.71	188.05 ± 34.16	197.37 ± 37.7
High density lipoprotein cholesterol (*M* mg/dl ± SD)	44.85 ± 10.03	45.05 ± 9.92	43.73 ± 10.26
Triglyceride (*M* mg/dl ± SD)	159.97 ± 105.54	146.9 ± 95.73	190.22 ± 115.38

Abbreviations: M, mean value; SD, standard deviation. *Individuals who are not using hypertensive medications. **Controls (normotensive), SBP < 120 mmHg and DBP < 80 mmHg; Cases (hypertensive), SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or antihypertensive medication.

SNPs were validated in the NCBI database (http://www.ncbi.nlm.nih.gov). The clinical information and genotype data that we used were graciously provided by the Center for Genome Science, KNIH, Korea Center for Disease Control (KCDC).

In silico replication

For *in silico* replication, we had plotted the *P* value of *SLC4A4* region using LocusZoom version 1.1 (http://csg.sph.umich.edu/locuszoom/), which is a tool to plot regional association results from genome-wide association scans or candidate gene studies (Pruim et al., 2010). Among the available GWAS results, SBP and DBP association results of the International Consortium of Blood Pressure Genome-Wide Association Studies (ICBP-GWAS) were used and confirmed the association with *SLC4A4* gene and blood pressure in the KARE. The ICBP-GWAS aims to further the understanding of the genetic architecture underlying blood pressure. The initial publication by this consortium studied SBP and DBP with discovery GWAS among 69,395 people and a combined sample of ~200,000 Europeans (Wain et al., 2011).

Statistical analysis

Most statistical analyses were performed using PLINK version 1.07 (http://pngu.mgh.harvard.edu/~purcell/plink) and PASW Statistics version 17.0 (SPSS Inc., Chicago, IL, USA). Linear regression was used to analyze SBP and DBP as quantitative traits in the final 7551 subjects, controlling for cohort, age, sex and body mass index (BMI) as covariates. The 37 selected SNPs were also analyzed in hypertension case-control studies using logistic regression analysis.

All association tests were based on an additive genetic model, and *P*-values were not adjusted for multiple tests. Statistical significance was determined at a two-tailed value of $P < 0.05$.

RESULTS

Association analysis with SNPs in *SLC4A4* gene and blood pressure traits

We informed the *SLC4A4* gene and its 37 SNPs (Table 2). And, the basic characteristics of study subjects were shown to Table 1. The mean age of the 7,551 study subjects was 51.44 years. The mean SBP of the 7,551 subjects was 115.65 ± 17.25, and the mean DBP was 74.21 ± 11.27 (Table 1). And, the mean and variance of BMI, SBP, DBP, total cholesterol, high density lipoprotein cholesterol, and triglyceride were all statistically different between case-control groups by Student's T-test in Table 1.

Linear regression analysis was used to associate genotypes with blood pressure traits, controlling for age, sex, BMI, and cohort as covariates. The results of associations

Table 2. The association results of SNPs in *SLC4A4* gene with blood pressure traits and/or hypertension

SNP	MAF	Function	SBP		DBP		HTN	
			beta	Additive *P*	beta	Additive *P*	OR (95% CI)	Additive *P*
rs1817143	0.232	Intron	-0.127	0.676	-0.094	0.647	1.02 (0.93~1.13)	0.652
rs1349693	0.010	Intron	1.379	0.281	0.607	0.483	1.17 (0.77~1.77)	0.472
rs2579301	0.013	Intron	1.893	0.101	1.160	0.139	1.36 (0.94~1.96)	0.098
rs12506660	0.473	Intron	0.044	0.864	0.292	0.093	1.07 (0.98~1.16)	0.136
rs2045012	0.473	Intron	0.023	0.929	0.201	0.248	1.07 (0.98~1.16)	0.128
rs1563045	0.473	Intron	0.017	0.948	0.196	0.259	1.07 (0.98~1.17)	0.121
rs1319630	0.484	Intron	0.014	0.958	0.209	0.240	1.07 (0.98~1.16)	0.147
rs2602070	0.016	Intron	-0.817	0.417	0.189	0.782	0.90 (0.63~1.30)	0.578
rs2602072	0.015	Intron	-0.594	0.559	0.358	0.603	0.92 (0.64~1.33)	0.664
rs2363717	0.457	Intron	0.086	0.736	0.188	0.278	1.08 (0.99~1.17)	0.086
rs6847284	0.016	Intron	-0.679	0.496	0.204	0.763	0.89 (0.63~1.27)	0.531
rs6826731	0.016	Intron	-0.713	0.472	0.262	0.697	0.91 (0.64~1.29)	0.592
rs2579326	0.016	Intron	-0.602	0.549	0.255	0.708	0.90 (0.63~1.29)	0.571
rs1542306	0.178	Intron	-0.020	0.953	-0.043	0.849	0.89 (0.80~1.00)	**0.046**
rs980363	0.458	Intron	0.096	0.710	0.160	0.361	0.97 (0.89~1.06)	0.514
rs2602049	0.253	Intron	0.394	0.176	0.369	0.062	1.10 (1.00~1.22)	**0.042**
rs1901712	0.211	Intron	0.503	0.107	0.373	0.077	1.10 (0.99~1.22)	0.074
rs1377281	0.010	Intron	0.039	0.976	-0.637	0.469	1.11 (0.72~1.70)	0.646
rs16846228	0.211	Intron	0.587	0.060	0.402	0.057	1.10 (0.99~1.22)	0.064
rs16846246	0.219	Intron	0.625	**0.041**	0.415	**0.045**	1.10 (0.99~1.21)	0.074
rs980519	0.219	Intron	0.578	0.060	0.383	0.066	1.10 (0.99~1.22)	0.067
rs16846302	0.116	Intron	-0.205	0.608	-0.266	0.325	0.90 (0.79~1.03)	0.131
rs4353874	0.170	Intron	-0.075	0.826	-0.091	0.695	0.99 (0.88~1.11)	0.807
rs4130912	0.037	Intron	-0.384	0.575	0.054	0.908	1.20 (0.96~1.49)	0.103
rs12511966	0.233	Intron	0.138	0.653	0.103	0.619	0.99 (0.89~1.10)	0.829
rs1134115	0.411	Intron	0.064	0.812	0.094	0.605	1.00 (0.91~1.09)	0.923
rs16846392	0.012	Intron	0.920	0.429	0.044	0.955	1.08 (0.73~1.59)	0.701
rs4458426	0.046	Intron	-0.571	0.364	-0.097	0.819	1.20 (0.98~1.46)	0.073
rs4235093	0.372	Intron	0.140	0.599	0.091	0.616	0.97 (0.89~1.06)	0.503
rs6846301	0.129	Intron	0.839	**0.032**	0.588	**0.027**	1.23 (1.09~1.40)	**1.2×10^{-3}**
rs4469035	0.499	Intron	0.500	0.053	0.373	**0.032**	1.06 (0.98~1.16)	0.166
rs6447031	0.373	Intron	0.151	0.568	0.098	0.584	0.97 (0.89~1.06)	0.568
rs7680649	0.394	Intron	0.481	0.076	0.293	0.111	1.08 (0.99~1.18)	0.087
rs12504851	0.394	Intron	0.460	0.080	0.284	0.110	1.09 (0.99~1.18)	0.068
rs7677525	0.172	Intron	0.481	0.161	0.216	0.354	1.03 (0.92~1.16)	0.601
rs1026305	0.038	Intron	-0.244	0.723	0.070	0.880	1.09 (0.87~1.36)	0.453
rs4694401	0.018	Intron	0.054	0.957	-0.358	0.594	0.93 (0.67~1.28)	0.644

Abbreviations: SNP, single nucleotide polymorphism; MAF, minor allele frequency; beta, regression coefficient; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension. Statistically significant values ($P < 0.05$) are indicated in bold type

on the 37 SNPs of *SLC4A4* gene were listed in Table 2.

The results on the SBP, two SNPs (rs16846246, rs6846301) were significantly associated with SBP (Table 2). The SNP rs6846301 had the significance *P* value

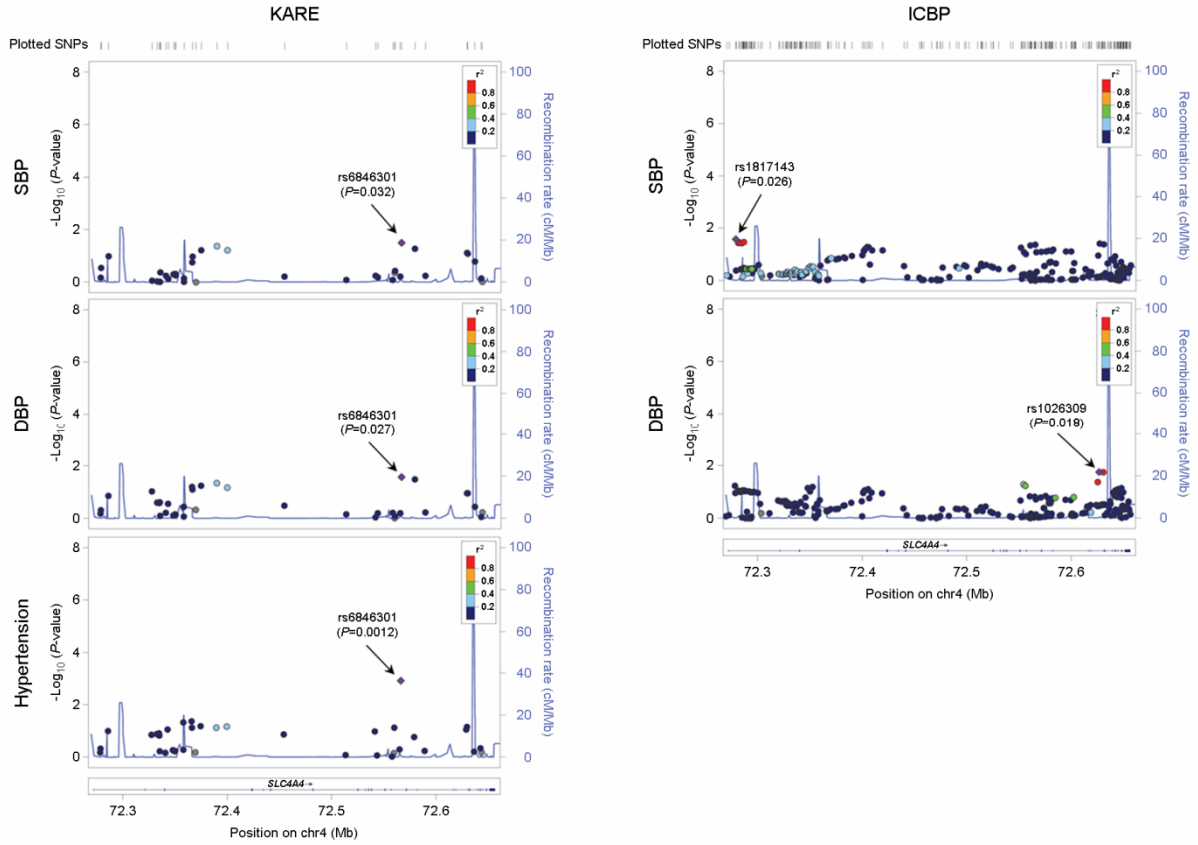

Fig. 1. Regional association plots of the SNPs in *SLC4A4* gene with systolic blood pressure, diastolic blood pressure and hypertension status in the KARE (Korean population in the Korean Association Resource) and the ICBP (International Consortium of Blood Pressure Genome-Wide Association Studies). Statistical significance of each SNP shown on the -$\log_{10}$ scale as a function of chromosome position (NCBI build 36). The sentinel SNP at each locus is shown in blue; the correlations (r^2) of each of the surrounding SNPs to the sentinel SNP are shown in the colors indicated in the key. Fine-scale recombination rate is shown in blue. The KARE cohort used the JPT + CHB Hapmap genotyping panel and the ICBP used the CEU Hapmap genotyping panel. Gene and SNP positions are indicated at the bottom.

(β=0.839, additive *P*=0.032). The results on the DBP, three SNPs (rs16846246, rs6846301, and 4469035) were significantly associated with DBP (Table 2). The SNP rs6846301 had the highest significance *P* value (β=0.588, additive *P*=0.027). The SNP rs6846301 had commonly significance in both SBP and DBP, and their effects showed the same directions.

Association analysis with SNPs in *SLC4A4* gene and hypertension

The 3 SNPs (rs1542306, rs2602049, and rs6846301) of *SLC4A4* were associated with hypertension status. The highest significant SNP in hypertension was rs6846301 (OR=1.23, CI: 1.09~1.40, additive $P=1.2 \times 10^{-3}$) (Table 2). Furthermore, the SNP rs6846301 was consistently associated with both blood pressure and hypertension (Table 2). And the SNP rs6846301 in *SLC4A4* gene was the highest signal in all phenotypes; SBP, DBP, and hypertension (Table 2, Fig. 1).

DISCUSSION

In this study, we had investigated the genetic variation of *SLC4A4* gene are associated with blood pressure and hypertension in the 7551 Korean subjects (Table 1). As a result, we investigated 37 SNPs with both blood pressure and hypertension (Table 2, Fig. 1). Moreover, the SNP rs6846301 had positive beta values in blood pressure, and those means that the carrier of minor allele had high blood pressure, and also susceptible for hypertension. Therefore

the SNP rs6846301 would be contributed high value of blood pressure, and promote the pathogenesis of hypertension.

Limitations of this study included the lack of detailed covered SNPs in the *SLC4A4* gene, and it is possible that multiple rare polymorphisms in the biological and positional candidate genes that were not included in this study could influence high BP. Because of having been the other association report of between *SLC4A4* gene and blood pressure, we did not correct for multiple tests in this study. But, we cope with the situation using *in silico* replication on published genotyping data. The results of ICBP-GWAS were showed significant association between the *SLC4A4* gene polymorphisms and blood pressures (SBP, DBP) (Fig. 1). Consequently, this report has the value of association study for *SLC4A4* and blood pressure traits.

SLC4A4, which encodes the electrogenic sodium bicarbonate cotransporter 1 on 4q21, gene is associated with decreased body weight/size, hematocrit, and abnormal ion homeostasis in mice (Gawenis et al., 2007). In addition, *SLC4A5* is a member of the same family of solute carriers as *SLC4* and was also shown to be associated with blood pressure (Hunt et al., 2006) and with hypertension (Taylor et al., 2009). Of the 4 SNPs on the sodium bicarbonate cotransporter gene (*SLC4A5*), rs8179526 had a statistically significant interaction with cytosine/thymine (C/T) genotype by sodium status on systolic BP (SBP; P=0.0077). A gene-environmental interaction with rs8179526 has a protective effect on SBP in African-American women with high sodium intake (Taylor et al., 2009).

Although the exact mechanism whereby the *SLC4A4* gene polymorphism may affect the vasculature is unclear, it is possible that this variant alters *SLC4A4* transcript length or RNA splicing causing significant heterogeneity in *SLC4A4* mRNA transcripts. The mRNA levels of *SLC4A4* (encoding electrogenic Na^+-HCO_3^- cotransporter) gene was increased by aortic constriction, so Yamamoto et al. reported that the pressure overload hypertrophy has enhanced activity of ventricular Na^+-HCO_3^- cotransporter (Yamamoto et al., 2007). Li et al. identified that the Na^+-HCO_3^- cotransporter NBC1 (*SLC4A4*, kidney specific) has acquired specific signals for targeting to the basolateral membrane (Li et al., 2007). Sodium bicarbonate cotransporter levels and *SLC4A4* gene polymorphisms seem to play a determinant role in the pathogenesis of hypertension.

From our research, genetic association of the *SLC4A4* gene has been searched in the genetic association databases (HuGe Navigator: http://hugenavigator.net). They had presented that the *SLC4A4* gene polymorphisms associated with the edema, ileus, cystic fibrosis, type 2 diabetes mellitus, cardiovascular disease etc including hypertension. Yang *et al*. had reported that the *SLC4A4* gene was exhibited differential allelic distributions and differential transcriptions between patient and control groups, and was confirmed by replication study as hypertension susceptibility gene (Yang et al., 2012). The other article had published that the polymorphisms of *SLC4A5* were associated with BP and with hypertension (Hunt et al., 2006; Taylor et al., 2009). These reports are in accord with our results for the *SLC4A4* gene's SNPs were associated with blood pressure traits.

Hypertension susceptibility gene, *SLC4A4*, was not only identified gene-based association scan and gene expression analysis in Han Chinese (Yang et al., 2012), but was also replicated by a KARE and ICBP-GWAS. Consequently, these results indicate that the *SLC4A4* gene is associated with blood pressures and hypertension status among the Asian and Caucasian population.

In summary, this study confirmed common genetic variation in *SLC4A4*, to be associated with blood pressure levels and risk of hypertension. And, we found statistically significant SNPs that are associated with blood pressure traits. Therefore, this study suggests *SLC4A4* gene polymorphism is significantly associated with hypertension susceptibility in Korean men.

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