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Original Article

Gender-specific Association of the *ANO1* Genetic Variations with Hypertension

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Development of hypertension is caused by complex contributions of genetic and environmental factors. In spite of the increased understanding of hypertension, genetic factors that contribute to hypertension largely remain elusive. *ANO1* gene encoding a calcium-activated chloride channel has recently been reported to affect spontaneous hypertension in the animal model. In this report, we investigated possible association of the *ANO1* gene with hypertension in human with *ANO1* variants found in Korean population. Fourteen polymorphisms of *ANO1* gene were analyzed to be associated with hypertension. Interestingly, the six polymorphisms that showed statistically significant association were all the male subjects. The highest significant SNP was rs7127129 (OR=1.14, CI: 1.02~1.28, additive *P*=0.023; OR=1.24, CI: 1.03~1.49, dominant *P*=0.025), and other five SNPs (rs2509153, rs11235473, rs10751200, rs10898827 and rs10899928) were also statistically associated with hypertension. Consequently, we found that the genetic variants of *ANO1* present statistically significant associations with hypertension in human, especially, in male. To the best of our knowledge, this study is the first report describing association of genetic polymorphisms of *ANO1* with hypertension in human.

Key Words: Hypertension, Calcium-activated chloride channel, *ANO1*, SNP, Association

INTRODUCTION

Hypertension is a status having consistent high blood pressure. Development of hypertension is caused by complex contributions of genetic and environmental factors. According to 'the Korea National Health and Nutrition Examination Survey (KNHANES)', prevalence of hypertension in Korean adult population has reached to 27.3%, which is almost similar with the prevalence of Americans (Horowitz et al., 2015) and is still growing. Seriousness of hypertension is its strong relationships with other metabolic diseases such as diabetes, obesity, dyslipidemia, and so on (Taylor et al., 2013; Kelly et al., 2014). In spite of its seriousness, genetic factors that are related with hypertension are still remains elusive. Hypertension studies with genetic information have been reported using KARE (Korean Association REsource) cohorts, such as Genome-wide association study (Cho et al., 2009), nonsynonymous SNPs association study (Hong et al., 2010), replication association study (Hong et al., 2009 & Jin et al., 2012), and candidate genes study (Jin et al., 2010).

Blood pressure is determined by combination of cardiac output and resistances of peripheral blood vessels (Marc and Llorens-Cortes, 2011). Therefore, when the cardiac output is consistent, blood pressure is determined mainly by vascular contractions. Contraction of vascular smooth muscle cells are controlled by combinatorial functions of several ion channels, among which *ANO1* gene (anoctamin 1), a calcium-activated chloride channel (CaCC), has been

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suspected as a causal genetic factor for the development of hypertension (Large and Wang, 1996; Heinze et al., 2014). The *ANO1* gene located on human chromosome 11q13.3, and induces smooth muscle contraction by transporting chloride ion. Calcium activates ANO1 (anion channel) in plasma membrane to efflux chloride ion (Cl^-) out of the cell by resulting in depolarization in the vascular smooth muscle cell. To compensate the chloride efflux, voltage-dependent Ca^{2+} channels lead influx of extracellular Ca^{2+} into the cytosol. Therefore, ANO1 overexpression could give rise to stronger arterial contraction and an increase of blood pressure. Actually, it has been reported that over-expression of *ANO1* contributed to spontaneous hypertension in the spontaneously hypertensive male rats (SHRs) (Wang et al., 2015) which suggests *ANO1* might be a novel genetic factor for hypertension.

We aimed to investigate whether genetic variations of *ANO1* gene are associated with hypertension in humans. For this purpose, the 14 single nucleotide polymorphisms (SNPs) of *ANO1* were collected from the Korean Association REsource (KARE) and were analyzed for their relationship with hypertension. Based on the results, we suggest that *ANO1* could be a susceptible gene for hypertension in human males.

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). Briefly 10,038 persons in the Ansung-Ansan prospective community cohorts were recruited. A two-community cohort study in South Korea was initiated beginning in 2001 as part of a major project for the Korean Health and Genome Study (KHGS) in Korea National Health and Genome Study (KNIH). Of the initial 10,038 subjects who were aged 40 to 69 years, 1196 were excluded due to poor genotyping data. In addition, to analyze accurate blood pressure traits, 330 subjects who were on drug treatments such as folk medicine that were likely to influence the blood pressure were also excluded. The remaining 8512 subjects were finally investigated in this study.

A case-control study was performed between hypertensive male cases (n = 910) and normotensive male controls (n = 2062). Hypertensive male cases were categorized with the systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg in addition to the subjects who were receiving hypertension medication. Normotensive male controls were defined as SBP < 120 mmHg and DBP < 80 mmHg. For quantitative blood pressure traits analysis, subjects who were undergoing antihypertensive treatment were excluded and the remaining 3747 males were investigated. 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.

Clinical characteristic measurement

Blood sample were drawn for biochemical measurements [triglyceride, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL)]. 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 SNPs

The detailed genotyping, quality control processes and quantitative traits including SBP and DBP were described in the previous report (Cho et al., 2009). 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 and Speed, 2006). Samples that had genotyping accuracies were lower than 98%, high missing genotype call rates (≥4%), high heterozygosity (>30%), or gender biases were excluded.

Table 1. Basic characteristics of the male subjects in the KARE study cohort

Characteristics	Quantitative trait analysis*	Case-control analysis**		
		Normotensive	Hypertensive	*P* value***
Number of subjects	3747	2062	910	
Age (*M* years ± *SD*)	51.27 ± 8.68	49.66 ± 8.17	55.06 ± 8.72	< 0.0001
Body mass index (BMI) (*M* kg/m^2 ± *SD*)	24.14 ± 2.9	23.82 ± 2.76	24.99 ± 3.01	0.008
Systolic blood pressure (SBP) (*M* mmHg ± *SD*)	116.5 ± 16.17	105.57 ± 8.64	137.56 ± 16.27	< 0.0001
Diastolic blood pressure (DBP) (*M* mmHg ± *SD*)	75.76 ± 10.99	68.94 ± 7.62	88.12 ± 10.37	< 0.0001
Total cholesterol (*M* mg/dl ± SD)	191.33 ± 36.24	190.44 ± 34.63	193.89 ± 38.25	0.004
High density lipoprotein cholesterol (*M* mg/dl ± SD)	43.79 ± 9.99	43.5 ± 9.68	43.35 ± 10.29	0.051
Low density lipoprotein cholesterol (*M* mg/dl ± SD)	114.26 ± 33.40	115.76 ± 31.86	112.73 ± 35.48	0.001
Triglyceride (*M* mg/dl ± SD)	176.66 ± 119.48	163.73 ± 110.17	202.42 ± 127.02	< 0.0001

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. ***Significant differences in characteristics between the normotensive and hypertensive subjects were determined by the two-tailed Student's *t*-test.

The 14 SNPs that we analyzed were selected from the KARE data, based on their positions within the *ANO1* gene boundary (5 kb upstream and downstream of the first and last exons, respectively) (Table 2). The positions of the SNPs were validated in the NCBI human genome build 36. For the *in silico* functional analysis, we used HaploReg v3 (http://www.broadinstitute.org/mammals/haploreg/haploreg_v3.php), which is a tool for exploring annotations of the noncoding variants. 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).

Statistical analysis

Most statistical analyses were performed using PLINK version 1.07 (http://pngu.mgh.harvard.edu/~purcell/plink) and PASW Statistics version 18.0 (SPSS Inc., Chicago, IL, USA). The 14 selected SNPs were also analyzed in hypertension case-control studies using logistic regression analysis, controlling for cohort, age and body mass index (BMI) as covariates. Linear regression was used to analyze for the clinical characteristics as quantitative traits in the final 3747 men, controlling for cohort, age and body mass index (BMI) as covariates. The association tests were based on an additive, dominant, and recessive genetic model, and *P*-values were not adjusted for multiple tests. Statistical significance was determined at a two-tailed value of $P < 0.05$. For the regional association plot, we had used the SNP Annotation and Proxy Search (SNAP) database (http://www.broadinstitute.org/mpg/snap/) using the CHBJPT (Chinese and Japanese) population panel originated from HapMap database for the recombination rate.

RESULTS

Association analyses between SNPs in *ANO1* gene and hypertension in male

Clinical characteristics of the study subjects were listed in Table 1. Mean age of the hypertensive males (n=910), mean systolic blood pressure (SBP), and mean diastolic blood pressure (DBP) was 55.06 years, 137.56 ± 16.27, and 88.12 ± 10.37 (Table 1), respectively. Means and variances of BMI, SBP, DBP, total cholesterol, LDL, and triglyceride were statistically different between normotensive and hyper-

Table 2. The association analysis results of SNPs in the *ANO1* gene with the hypertension in the KARE males

No.	SNP	Minor allele	MAF	Function	Hypertension (controls 2062: cases 910)					
					OR (95% CI)	Add *P*	OR (95% CI)	Dom *P*	OR (95% CI)	Rec *P*
1	rs2509153	T	0.288	intron	1.11 (0.98~1.27)	0.107	1.08 (0.92~1.28)	0.334	1.36 (1.01~1.83)	**0.045**
2	rs2515274	T	0.145	intron	0.98 (0.83~1.15)	0.781	0.98 (0.81~1.17)	0.800	0.95 (0.52~1.73)	0.858
3	rs2509166	G	0.494	intron	1.07 (0.95~1.20)	0.253	1.06 (0.88~1.28)	0.534	1.13 (0.94~1.36)	0.205
4	rs2515267	T	0.412	intron	1.02 (0.91~1.15)	0.753	1.06 (0.89~1.26)	0.499	0.97 (0.78~1.21)	0.790
5	rs2509175	T	0.095	intron	0.96 (0.79~1.16)	0.657	1.00 (0.81~1.24)	0.996	0.42 (0.16~1.11)	0.080
6	rs948173	G	0.450	intron	0.99 (0.88~1.11)	0.847	0.97 (0.82~1.16)	0.769	1.00 (0.81~1.23)	0.999
7	rs1940236	A	0.232	intron	0.90 (0.78~1.04)	0.138	0.90 (0.76~1.06)	0.194	0.81 (0.55~1.19)	0.275
8	rs10160639	A	0.195	intron	1.08 (0.94~1.25)	0.287	1.04 (0.88~1.24)	0.646	1.50 (1.00~2.24)	0.051
9	rs10793024	T	0.154	intron	0.92 (0.78~1.08)	0.309	0.88 (0.73~1.06)	0.171	1.17 (0.70~1.96)	0.546
10	rs11235473	T	0.468	intron	1.14 (1.01~1.28)	**0.029**	1.21 (1.00~1.45)	**0.047**	1.17 (0.96~1.42)	0.115
11	rs10751200	G	0.226	intron	0.87 (0.76~1.01)	0.059	0.89 (0.75~1.05)	0.166	0.66 (0.44~0.99)	**0.046**
12	rs10898827	A	0.225	intron	0.88 (0.76~1.01)	0.065	0.89 (0.75~1.06)	0.184	0.66 (0.44~0.99)	**0.045**
13	rs10898828	G	0.226	intron	0.87 (0.76~1.00)	0.057	0.89 (0.75~1.05)	0.161	0.66 (0.44~0.99)	**0.046**
14	rs7127129	G	0.475	intron	1.14 (1.02~1.28)	**0.023**	1.24 (1.03~1.49)	**0.025**	1.16 (0.95~1.40)	0.140

Abbreviations: SNP, sigle nucleotide polymorphism; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; Add *P*, additive genetic model *P* value; Dom *P*, dominant genetic model *P* value; Rec *P*, recessive genetic model *P* value. Controls were the subjects with SBP < 120 mmHg and DBP < 80 mmHg, and hypertension cases were the subjects with SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or antihypertensive medication. Statistically significant values ($P < 0.05$) are indicated in bold and underline.

tensive groups by Student's *t*-test (Table 1). Minor allele, minor allele frequency, and function of *ANO1* gene and its 14 SNPs were presented (Table 2). Regional association plots for the 14 SNPs in the *ANO1* were presented (Fig. 1).

The six SNPs of *ANO1* were associated with hypertension status. One of the six SNPs, rs7127129, had the highest significance with the hypertension (OR=1.14, CI: 1.02~1.28, additive *P*=0.023, Table 2). The significance of the rs7127129 in hypertension was statistically meaningful in additive and dominant genetic models (OR=1.24, CI: 1.03~1.49, dominant *P*=0.025, Table 2). The five other SNPs (rs2509153, rs11235473, rs10751200, rs10898827 and rs-10899928) were also associated with the hypertension (Table 2). Among the six SNPs, rs10751200, rs10898827, and rs10898828 showed resistance to the hypertension (OR<1), and were composed in one LD block (r^2>0.99). Otherwise, rs11235473 and rs7127129 were susceptible to hypertension (OR>1), and had high correlation with each other (r^2>0.99).

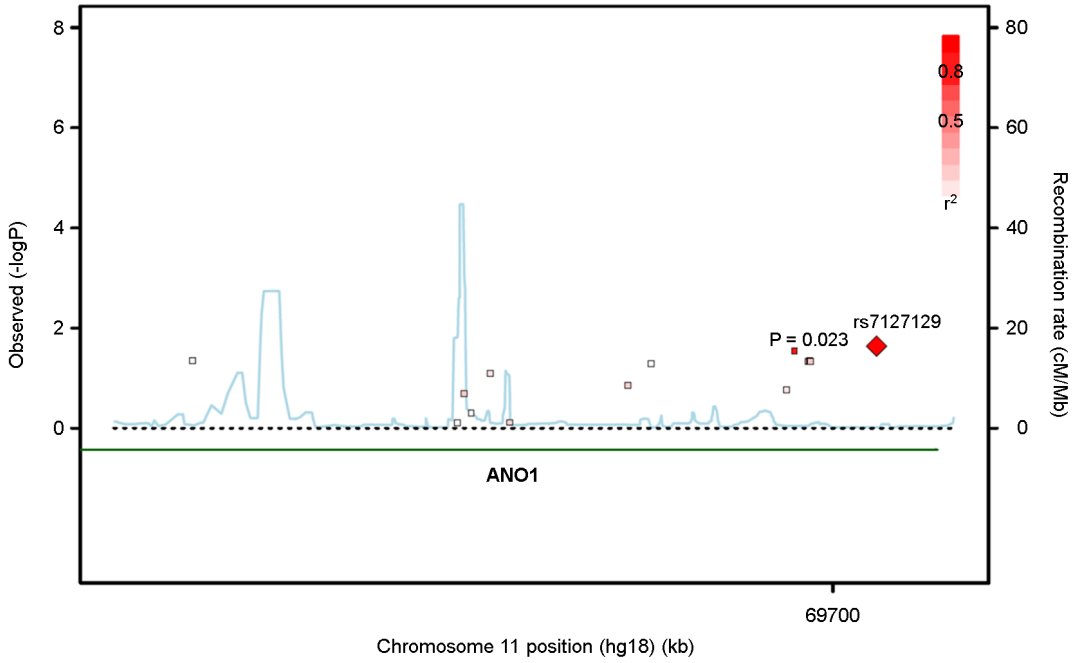

Fig. 1. The regional association plots for the 14 SNPs in the *ANO1* gene were generated with SNAP database (http://www.broadinstitute.org/mpg/snap/) for the association results for gene annotations, and estimated recombination rates. The probability values were chosen among the highest values of the three genetic model.

Table 3. The association analysis results of 6 SNPs in the *ANO1* gene with total cholesterol, HDL and LDL in the KARE males (n=3,747)

SNP	Minor allele	MAF	Function	Total cholesterol		HDL		LDL	
				beta ± se	Dom *P*	beta ± se	Rec *P*	beta ± se	Dom *P*
rs2509153	T	0.288	intron	2.57 ± 1.13	**0.024**	-0.11 ± 0.60	0.854	2.97 ± 1.05	**4.8×10^{-3}**
rs11235473	T	0.468	intron	0.51 ± 1.25	0.681	-0.72 ± 0.39	0.067	0.98 ± 1.16	0.398
rs10751200	G	0.226	intron	0.08 ± 1.15	0.947	0.65 ± 0.75	0.390	-0.12 ± 1.07	0.909
rs10898827	A	0.225	intron	-0.12 ± 1.16	0.921	0.66 ± 0.75	0.380	-0.29 ± 1.08	0.790
rs10898828	G	0.226	intron	0.03 ± 1.15	0.977	0.65 ± 0.75	0.390	-0.16 ± 1.07	0.884
rs7127129	G	0.475	intron	0.56 ± 1.25	0.653	-0.85 ± 0.39	**0.027**	0.87 ± 1.17	0.456

Abbreviations: SNP, sigle nucleotide polymorphism; MAF, minor allele frequency; beta, regression coefficient; se, standard error; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; Dom *P*, dominant genetic model *P* value; Rec *P*, recessive genetic model *P* value. Statistically significant values ($P<0.05$) are indicated in bold and underline.

Association analyses between the six SNPs in *ANO1* gene and the clinical characteristics

The six SNPs having association with the hypertension were further analyzed for the analysis with quantitative traits. The male subjects' clinical characteristics were collected such as SBP, DBP, total cholesterol, HDL, LDL, and triglyceride (Table 1). Linear regression analysis was used to analyze associations between the SNPs and the clinical characteristics by controlling for age, BMI, and cohort as covariates. The two SNPs (rs2509153 and rs7127129) were significantly associated with the clinical characteristics. The rs2509153 was associated with both total cholesterol (β= 2.57, dominant *P*=0.024) and LDL (β=2.97, dominant *P*=

Table 4. The association analysis results of SNPs in the *ANO1* gene with the hypertension in the KARE females

No.	SNP	Minor allele	MAF	Function	Hypertension (controls 2390: cases 1058)					
					OR (95% CI)	Add *P*	OR (95% CI)	Dom *P*	OR (95% CI)	Rec *P*
1	rs2509153	T	0.276	intron	0.99 (0.87~1.13)	0.917	0.96 (0.81~1.13)	0.635	1.10 (0.82~1.49)	0.529
2	rs2515274	T	0.144	intron	1.19 (1.01~1.40)	**0.039**	1.19 (0.99~1.44)	0.064	1.49 (0.87~2.56)	0.147
3	rs2509166	G	0.493	intron	1.03 (0.91~1.16)	0.671	0.98 (0.81~1.18)	0.830	1.10 (0.90~1.33)	0.354
4	rs2515267	T	0.421	intron	0.99 (0.88~1.11)	0.829	0.94 (0.79~1.12)	0.488	1.06 (0.85~1.31)	0.634
5	rs2509175	T	0.091	intron	0.96 (0.79~1.17)	0.680	0.93 (0.75~1.16)	0.535	1.27 (0.59~2.72)	0.547
6	rs948173	G	0.450	intron	0.99 (0.88~1.11)	0.858	0.98 (0.82~1.17)	0.785	1.00 (0.81~1.23)	0.997
7	rs1940236	A	0.240	intron	0.96 (0.84~1.10)	0.563	0.96 (0.81~1.13)	0.600	0.93 (0.64~1.34)	0.700
8	rs10160639	A	0.191	intron	0.98 (0.84~1.13)	0.758	0.95 (0.80~1.13)	0.549	1.16 (0.74~1.81)	0.526
9	rs10793024	T	0.161	intron	0.95 (0.81~1.10)	0.478	0.92 (0.77~1.10)	0.372	1.05 (0.65~1.69)	0.850
10	rs11235473	T	0.462	intron	0.99 (0.88~1.11)	0.837	1.03 (0.86~1.23)	0.791	0.94 (0.77~1.14)	0.516
11	rs10751200	G	0.234	intron	0.95 (0.83~1.09)	0.458	0.94 (0.80~1.11)	0.485	0.92 (0.64~1.33)	0.662
12	rs10898827	A	0.233	intron	0.95 (0.83~1.09)	0.464	0.94 (0.80~1.12)	0.490	0.92 (0.64~1.34)	0.666
13	rs10898828	G	0.234	intron	0.95 (0.83~1.10)	0.511	0.95 (0.80~1.12)	0.515	0.94 (0.65~1.36)	0.750
14	rs7127129	G	0.470	intron	0.99 (0.88~1.11)	0.886	1.06 (0.88~1.27)	0.559	0.91 (0.75~1.12)	0.377

Abbreviations: SNP, sigle nucleotide polymorphism; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; Add *P*, additive genetic model *P* value; Dom *P*, dominant genetic model *P* value; Rec *P*, recessive genetic model *P* value. Controls were the subjects with SBP < 120 mmHg and DBP < 80 mmHg, and hypertension cases were the subjects with SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or antihypertensive medication. Statistically significant values ($P<0.05$) are indicated in bold and underline.

4.8×10^{-3}). On the other hand, the rs7127129 was associated with HDL (β=-0.85, recessive *P*=0.027). The six SNPs had no association with the characteristics indicating blood pressures such as SBP, and DBP.

Association analyses between the SNPs in *ANO1* gene and the hypertension in female

Additionally, association between the genetic variations of *ANO1* gene and hypertension in female was examined. The SNPs had no significant association with the hypertension except the rs2515274 (OR=1.19, CI: 1.01~1.40, additive *P*=0.033, Table 4). These results indicate there is gender-specific association between the SNPs in *ANO1* gene and hypertension.

DISCUSSION

In this study, we investigated the association of genetic variations of *ANO1* gene with hypertension in the Korean population. The six SNPs of *ANO1* were associated with

hypertension in a gender-specific manner (Table 2, Fig. 1). Among the six SNPs, the two SNPs were also associated with total cholesterol, LDL, or HDL (Table 3). The six SNPs were analyzed *in silico* using HaploReg v3 which presented the motif changes in all of the six SNPs (Table S1). On the other hand, the 14 SNPs of *ANO1* had no relationship with hypertension in the Korean females except one SNP (Table 4). Unlike the hypertension results, we were not able to find relationships between the genetic variations of *ANO1* gene and SBP and/or DBP. Whereas, ANO1 had been shown to have a relationship with blood pressure in the experiments with SHRs (Wang et al., 2015). The discordance might be caused by limited number of subjects (79 male subjects) having blood pressure above 160 mmHg and heterogeneous reasons for the hypertension. Therefore, it will be necessary to collect increased number of subjects having high blood pressure and select hypertensive subject caused by arterial resistance in the future study.

Our statistical results showed a gender-specific association of the SNPs in the *ANO1* gene with hypertension in the male (Tables 2 and 4). Several gender-specific associations of the SNPs with hypertension have been reported: association of *AGT* polymorphisms with hypertension in female (Dhanachandra Singh et al., 2014), association of *ESR1* polymorphisms with hypertension in male (Kelly et al., 2013), and association of *KNG1* polymorphisms with essential hypertension in male (Zhao et al., 2009). In a recent study, significant gender-specific differences in concentration of serum metabolites and the metabolism-related genes have been revealed (Mittelstrass et al., 2011). Nevertheless, the accurate mechanisms of these gender-specific associations of genetic polymorphisms still remain to be clarified.

We further analyzed the influence of smoking to the high prevalence of hypertension in the males. Smoking status is very different between Korean males and females. Korean females have low smoking habit (164 females, 3.52%), whereas Korean males show very high smoking habit (2,064 males, 49.34%) from KARE data. Case control analyses were conducted toward the male hypertension group having smoking habit or the non-smoking male hypertension group, separately. The results indicated that only the male hypertension group having smoking habit had association with the SNPs of *ANO1* gene: among the 14 SNPs of *ANO1* gene, three SNPs were associated with hypertension (Table S2). These results suggest that smoking could be a reason for the gender-specific differences.

Despite a couple of reports implicating the relationship between calcium-activated chloride channel and hypertension, there has been no report for the association between *ANO1* gene and hypertension in human. Even in the genetic association databases (HuGE Navigator: http://hugenavigator.net), we were not able to find any significant association of *ANO1* polymorphisms with metabolic disease. Therefore, this is the first report describing genetic polymorphisms in the *ANO1* gene associated with hypertension in human.

In summary, we investigated whether the *ANO1* gene associated with hypertension in Korean population. And, we found that the *ANO1* polymorphisms were statistically associated with hypertension in the Korean male subjects. Therefore, this study suggests that the *ANO1* gene could be a causal genetic factor for hypertension.

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Conflict of interest

The authors declare that they have no competing interests.

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