LETTER to the EDITOR

Association of ATP6AP2 Gene Polymorphisms with Essential Hypertension in a south Chinese Han Population

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Dear Editor

Essential hypertension is a highly heterogeneous disorder that is influenced by both genetic and environmental factors, as well as their interactions (Lifton et al.,2001). Recently, Genome-wide association studies with Japanese cohorts have revealed a new hypertension susceptibility gene, ATP6AP2, which encodes (pro) renin receptor, was associated with increased cardiovascular risks in humans (Krop et al., 2013). A functional polymorphism (5+169 C>T) was identified to be significantly associated with blood pressure in Japanese and Caucasian males (Hirose et al., 2009; Ott et al., 2011). And, the +1513A>G polymorphism was reported to be a risk factor of lacunar infarction and left ventricular hypertrophy in Japanese females (Hirose et al., 2011). However, all the reports were conducted in Caucasian and Japanese. Here, we reported a significant association between the ATP6AP2 rs5918007 and Essential hypertension in a south Chinese Han population.

The 1113 subjects(case vs. control: 561 vs. 552) aged 45-75 years of Chinese Han population were collected from Changsha province in China. Written informed consent for genetics analyses were included from all the participants in this study. The local Ethics Committee approved the study protocol. The diagnosis of hypertension was made according to a classification base on blood pressure levels 160/100mmHg. In addition, The 552 unrelated subjects who had blood pressure (BP)<140/90 mm Hg, no history of cardiovascular, diabetes mellitus or other diseases were considered as normotensive control. Distribution of Fasting plasma glucose (FPG) did not differ significantly between the two groups. Body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDL-C), Total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were significantly higher in EH group compared with the control group of each minority(P<0.05).

Genotypes of two well studied SNPs in ATP6AP2 (rs5918007 and rs6609080) gene were determined by a ligase detection reaction (LDR) method. Sequencing was performed in ABI3730XL. Statistical analyses were performed with SPSS 15.0. The alleles and genotype frequencies of ATP6AP2 between the patients and controls were compared using a Fisher's exact test. Statistical significance was set at p<0.05.

All variants in cases and controls were in HWE (p>0.05). No association was found between the ATP6AP2 rs6609080 and essential hypertension in Chinese Han (p>0.05). And the results didn't stratify when adjusted by gender (rs6609080: p= 0.531 in male and p=0.544 in female). In addition, analysis of the essential hypertension cohort revealed that the frequency of the ATP6AP2 rs5918007T was significantly higher in patients (0.441) than that controls (0.292) with a OR 1.653(p<0.001, 95%CI: [1.329-2.058]). However, the association was not significant in both male and female subgroups (p=0.675 for male and p=0.627 for female) (Table 1). Similar results were also observed in the frequency of TT+CT genotype (Receive model) and CC+CT genotype (Dominant model) in the EH cohort and controls (Table 2).

Further more, ATP6AP2 rs5918007 genotypes were found to be significantly associated with the SBP and age (p<0.01). No significant evidence of association between the ATP6AP2 rs5918007 and other clinical characters subgroups (FPG, BMI, HDL-C, TC and LDL-C) (p>0.05) (Table 3).

The genetic association between the (P)RR/ATP6ap2 gene and EH has only reported in Japanese and Caucasian. For the first time, we conducted a case-control study to investigate the association between ATP6ap2 polymorphisms and EH and find a significant association between rs5918007 and EH. Although significant association was reported in previous studies and present study, we couldn't confirm the association in both male and female subgroups. The limited samples in subgroups may explain it. Moreover, the mechanism that this polymorphism participated in the pathogenesis of EH is still unknown. Further research on the function of this SNP in effecting the development of EH is necessary.

Table 1. The Association between ATP6AP2 Alleles and Essential Hypertension

Gene	SNP rs, allele A > B	Alleles		p	ORa (95% CI)	P_{male}	P_{female}
		Cases(n=561) B	Controls(=552) B				
ATP6AP2	rs5918007 (C>T)	247(44.1%)	161(29.2%)	<0.001	1.65[1.33-2.06]	0.68	0.63
	rs6609080 (A>G)	276(49.2%)	290(52.5%)	0.05	0.82[0.67-0.99]	0.53	0.54

a OR and 95% CI are calculated for the minor allele of each SNP. SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence intervals

Table 3. The Association between rs5918007 and Clinical Features in Essential Hypertension

Genotypes	Clinical features								
	SBP (mmHg)	DBP (mmHg)	Age (Years)	BMI (kg/m^2)	FPG (mmol/L)	TC (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	TG (mmol/L)
CC	153.16±35.28	95.6±18.9	62.0±7.6	22.9±3.5	27.9±3.6	5.4±1.3	3.2±0.8	1.2±0.4	1.6±0.9
CT	146.13±21.48	91.6±16.9	60.4±7.4	23.5±3.5	27.7±4.6	5.3±1.2	3.3±0.5	1.3±0.4	1.7±1.7
TT	165.23±25.61	93.2±17.8	57.4±6.8	23.5±3.7	28.7±5.1	5.2±1.3	3.0±0.6	1.3±0.3	1.7±1.9
*P**	<0.01	0.45	0.009	0.73	0.39	0.64	0.25	0.39	0.59

Abbreviation: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: Fasting plasma glucose, HDL-C: high-density lipoprotein cholesterol, TC: Total cholesterol; LDL-C: low-density lipoprotein cholesterol, *P values from Student's t test or χ^2

Table 2. The Association between ATP6AP2 Genotypes and Essential Hypertension

SNP rs, allele A > B	Genotypes			Cases(n=561)		Controls(=552)	*P**	P_{male}	P_{female}	"Recessive model (AA/AB+BB)"		*P**	P_{male}	P_{female}	"Dominant model (BB/ AB+AA)"		*P**	P_{male}	P_{female}
	AA	AB	BB	AA	AB	BB				case	control				case	control			
rs5918007 (C>T)	276	243	42	198	222	132	<0.001	0.35	0.39	276/285	198/354	<0.0001	0.58	0.64	42/519	132/420	<0.0001	0.79	0.42
rs6609080 (A>G)	144	276	141	138	285	129	0.3	0.29	0.28	144/417	138/414	0.79	0.84	0.85	141/420	129/423	0.49	0.32	0.37

* P values from Student's t test or χ^2

Gender is one of the risk factors for hypertension. Sexual bias in hypertension has long been recognized in humans as well as in animal models. The sexual bias in hypertension may be caused by the differences in hormonal systems, social stress, life styles, and genetic determinants as well as their interactions (Rana et al., 2007). Here we identified ATP6AP2 rs5918007 as a new candidate SNP associated with hypertension in Chinese Han. However, the significant association disappeared in both male and female groups, suggesting the pathogenesis of EH is likely to be not different between male and female groups in Chinese Han population. We noted that significant association was detected between ATP6AP2 rs5918007 genotypes and clinical features in EH cohort. While this association didn't exist when adjusted by gender(P>0.05), which may due to the limited samples in male and female subgroup (Male: case vs. contro l: 357 vs. 333; female: case vs. control: 204 vs. 216). It reported that a gene may exert its gender-specific effects on blood pressure through interactions with other sex-related factors, such as hormones. This suggests that sex hormones are involved in the sexual dimorphism of hypertension associated with certain genes. Thus the levels of sex hormones in EH need to be taken into account.

In conclusion, the present results suggest that ATP6AP2 rs5918007T might be susceptible factors in Chinese Han population.

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