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RESEARCH ARTICLE

ASSOCIATION OF CDH13 (*rs7200009*) GENE POLYMORPHISM WITH ESSENTIAL HYPERTENSION IN SOUTH INDIAN POPULATION

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ABSTRACT

Hypertension (HT) is the most prevalent, complex quantitative trait which is characterized by chronic increase in the blood pressure. High blood pressure is one of the known risk factor for stroke, coronary artery disease, congestive heart failure, end-stage renal and cerebrovascular disease. Essential hypertension (EH) is the most common condition which contributes to ~ 95% of cases and has no clear single identifiable cause. Monogenic forms of hypertension, familial studies, twin studies and cross transplantational studies in experimental models have revealed the association of genetic components with essential hypertension. In view of this fact a case-control association study was conducted to investigate the possible involvement of *CDH13* (*rs7200009*) polymorphism in essential hypertensive patients. A total of 568 cases and 604 controls were recruited for this study. The SNP marker of *CDH13* gene (*rs7200009*) showed significant difference between the case and control groups in south Indian population studied. The genotype frequency was almost the same for both the case and control data sets. The result of the present study indicates that *CDH13* gene polymorphism (*rs7200009*) is associated with essential hypertension in south Indian population.

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INTRODUCTION

EH being a complex, quantitative trait is diverse across individuals. Ethnic and genetic heterogeneity influences variable clinical presentation and drug response in individuals making genetic study on hypertension to be a challenging task (Shih and O'Connor, 2008). The heritability of essential hypertension as suggested by twin and family studies is in the range of ~50% (Kupper *et al.,* 2006). Relative risk of hypertension when a sibling is affected the sibling's recurrence risk has been estimated as 2.5 to 3.5 (Tobin *et al.,* 2007). The variations in blood pressure that are genetically determined are termed as "inherited BP". Several other factors such as obesity, insulin resistance, smoking, high alcohol intake, high salt intake, low potassium and calcium intake, sedentary life-style, aging and stress, denoted as "hypertensinogenic" factors are known to elevate blood pressure. While, inherited blood pressure is considered to be the core BP, these hypertensinogenic factors tend to increase BP over and above the range of inherited BP (Carretero and Oparil, 2000). In view of the above mentioned facts, cadherin gene polymorphisms seemed to be an attractive target to unravel the genetic complexity of EH in south Indian population. Cadherins are a large family of transmembrane adhesion molecules which normally mediate calcium-dependent homophilic intercellular adhesion (Angst *et al.,* 2001). They are directly involved in a wide variety of processes such as cell adhesion, cell sorting, cell survival, morphogenesis, formation of intercellular junctions, maintenance of tissue integrity and tumourigenesis (Rowlands *et al.,* 2006). Calcium binding is essential for adherence function of cadherins, hence the name calcium dependent adherent protein. T-cadherin (T-cad) or truncated cadherin is a unique atypical cadherin, because it lacks transmembrane and cytoplasmic domains and is attached to the

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plasma membrane via a glycosylphosphatidylinositol (GPI) anchor. Though T-cad is expressed in various organs and tissues, expression is predominant in cardiovascular tissues such as heart, aorta, carotid, iliac and renal arteries (Ivanov *et al.,* 2001). Potential roles of this molecule include negative guidance of projecting axons in the embryonic nervous system, stimulation of angiogenesis and regulation of cell growth and migration (Philippova *et al.,* 2009).

T-Cadherin and angiogenesis

T-cad is known to affect angiogenic behavior of endothelial cells bidirectionally. The up-regulation and down regulation of T-cad is found to be proangiogenic (Philippova *et al.,* 2006; Ghosh *et al.,* 2007) and anti-angiogenic (Hebbard *et al.,* 2008) respectively. Angiogenesis by T-cad is influenced by hemophilic binding between the cells which reduces adhesion and increases migration which ultimately leads to the proliferation of endothelial cells. T-cad is found to be upregulated in several pathological conditions including atherosclerosis (Ivanov *et al.,* 2001), restenosis after ballon angioplasty (Kudrjashova *et al.,* 2002) and tumor angiogenesis (Wyder *et al.,* 2000).

T-Cadherin a receptor to adiponectin

Adiponectin (APN) is an adipocyte derived hormone with levels ranging from 5 - 30µg/ml in healthy individuals. Reduced plasma adiponectin levels were observed in patients with obesity (Weyer *et al.,* 2001), type 2 diabetes mellitus (Kondo *et al.,* 2002), hypertension (Iwashima *et al.,* 2004), myocardial infarction (Pischon *et al.,* 2004), ischemic stroke (Chen *et al.,* 2005) and coronary artery disease (Yang and Chuang, 2006). T-cadherin produced by cardiomyocytes is necessary for sequestering APN to heart. Experiments performed by Denzel *et al.* (2010), reported that ablation of T-cadherin expression dramatically increased levels of APN in the circulation. The excessive amount of APN was unable to associate with cardiac tissue and activate APN-dependent cardiac AMPK signaling, a major pathway associated with cardioprotective functions. On the other hand, APN deficiency suppressed T-cadherin expression which is evident from the fact that APN-KO mice exhibited low cardiac T-cadherin protein expression. Cardiac phenotype was rescued by restoring T-cadherin expression after the administration of recombinant APN to APN-KO mice. This association reactivated AMPK signaling and controlled cardiac injury. Absence of T-cad failed to rescue the phenotype. Thus, T-cadherin expressed on the surface of cardiomyocytes is necessary for the binding of APN and thereby facilitating cardioprotective functions. Recently, GWAS for genetic markers in determining plasma adiponectin value in Korean population reported that genetic variants in *CDH13* gene (coding T-cadherin), but not genetic variants in the *ADIPOQ* gene (coding for adiponectin), influence adiponectin levels in Korean adults (Jee *et al.,* 2010). The QTL on *CDH13* gene was also reported in Filipinos (Wu *et al.,* 2010) and more recently in a Chinese population (Chung *et al.,* 2011).

T-Cadherin and hypertension

GWAS performed in two European (Org *et al.,* 2009), and African-American populations (Adeyemo *et al,* 2009) has exposed a number of polymorphic markers in *CDH13* gene showing associations with EH. Kidambi *et al.* (2012), replicated the study conducted by Adeyemo *et al.* (2009) in an African-American population from the mid-western United States. Borderline associations were observed for two SNPs viz., *rs7200009* and *rs17177428* of *CDH13* gene. The former was found to be associated with systolic and diastolic BP, whereas the latter was associated with diastolic BP alone. Taken together, the information acquired from the GWAS and other functional studies denote *CDH13* a potential gene for further analysis with respect to the hypertension phenotype.

Methodology

All the samples were selected based on the 7th (2003) JNC report and WHOISH guidelines for management of hypertension (Chalmers *et al.,* 1999). The clinical investigations were carried out by qualified physicians and informed consent was obtained from all the patients and controls. Five ml of venous blood was collected from hypertensive patients (n = 568) and controls (n = 604) between the age group of 20-82 years. The baseline data of the subjects are given in table 1. Patients' samples were collected from four different areas: 1. Govt. Hospital, Headquarters Dindigul, Tamilnadu, 2. K.S. Hospital, Kilpauk, Chennai, Tamilnadu, 3. Government Hospital, Headquarters Chennai, Tamilnadu, India and 4. Voluntary Health Services, Adyar, Chennai, Tamilnadu, India. Age and sex matched control samples were collected from healthy volunteers and patients who visited outpatient clinics with minor ailments without hypertension in previous records. Patients with the history of diabetes mellitus, hyperlipidaemia, liver or renal disease, myocardial infarction and other causes of secondary hypertension were excluded from the study. All the subjects were recruited based on standard questionnaire and written informed consent was obtained. The study was approved by Institutional Human Ethical Committee.

Genotyping: Genomic DNA was extracted from the buffy coat of EDTA anti-coagulated blood by using Miller *et al.* (1988) salting out method. Genotype analysis for both the SNP marker was based on PCR-RFLP method. PCR was performed in mastercycler gradient (Eppendorf, Hamburg, Germany). PCR was performed in 20 µl volumes using 100ng of genomic DNA, 200µM of dNTP, 5pmol/µl of forward: VP24: 5'-ATTGGACACAGTATCCC-3' and reverse VP25: 5'-ATGTGAGTGATTCTGATGC-3' (Eurofins MWG Operon, Bangalore, India), 2mM $MgCl_2$ and 0.5U of Taq DNA polymerse (Prime Taq DNA polymerase, Korea) and was amplified following the PCR conditions which involves an initial denaturation at 94°C for 4 min, annealing at 54°C for 45 secs, extension at 72°C for 45 secs and a final extension at for 4 min. 5 µl of PCR product was checked on a 1% agarose gel. 15 µl of PCR product was digested using restriction enzyme *HaeIII* procured from New England Biolabs, England. Digestion was carried out at 37°C for 2 hours. The digested product was visualized on a 2% agarose gel and the results were documented. Sequencing analysis was performed to confirm genotypes and the sequence chromatograms (Fig. 1) were analyzed using CHROMAS 2.31 software (Technelysium, Australia). The comparison of allele

frequencies between different ethnic groups was performed from the data obtained from 1000 genome browser (http://browser.1000genomes.org/) (Fig. 2). *Statistical analysis:* All the continuous variables were expressed as mean ± standard deviation. Student's t-test was used for comparison of means of different variables. $\chi 2$ analysis was used to test for deviation of genotype distribution from Hardy-Weinberg equilibrium and to determine whether any significant differences in allele or genotype frequencies between cases and controls. The association between genotypes and hypertension risk was analyzed by calculating odds ratio (OR) at 95% confidence interval (95% CI). Statistical tests including logistic regression analysis were performed using the statistical package SPSS 14.0 version (SPSS Inc., Chicago, Illinois, USA). *P* value < 0.05 was considered to be statistically significant.

RESULTS

The genotypes and sequence chromatograms of the *CDH13* gene polymorphism *(rs7200009)* are shown in Figure 1. A comparative analysis for allele frequencies in different populations along with south Indian population is shown in figure 2. The allele frequency values of the study population (C-75% and T-25%) were found to be close to European population (C-84% and T-16%) than Asian population (C-95% and T-5%). A significant departure from Hardy-Weinberg equilibrium was observed in the genotype frequencies of both case and control groups ($p = <10^{-7}$) (Table 2). There was no significant difference between the genotype frequencies of the case and control groups which is evident from the p value of 0.088 was observed at χ^{2df}.

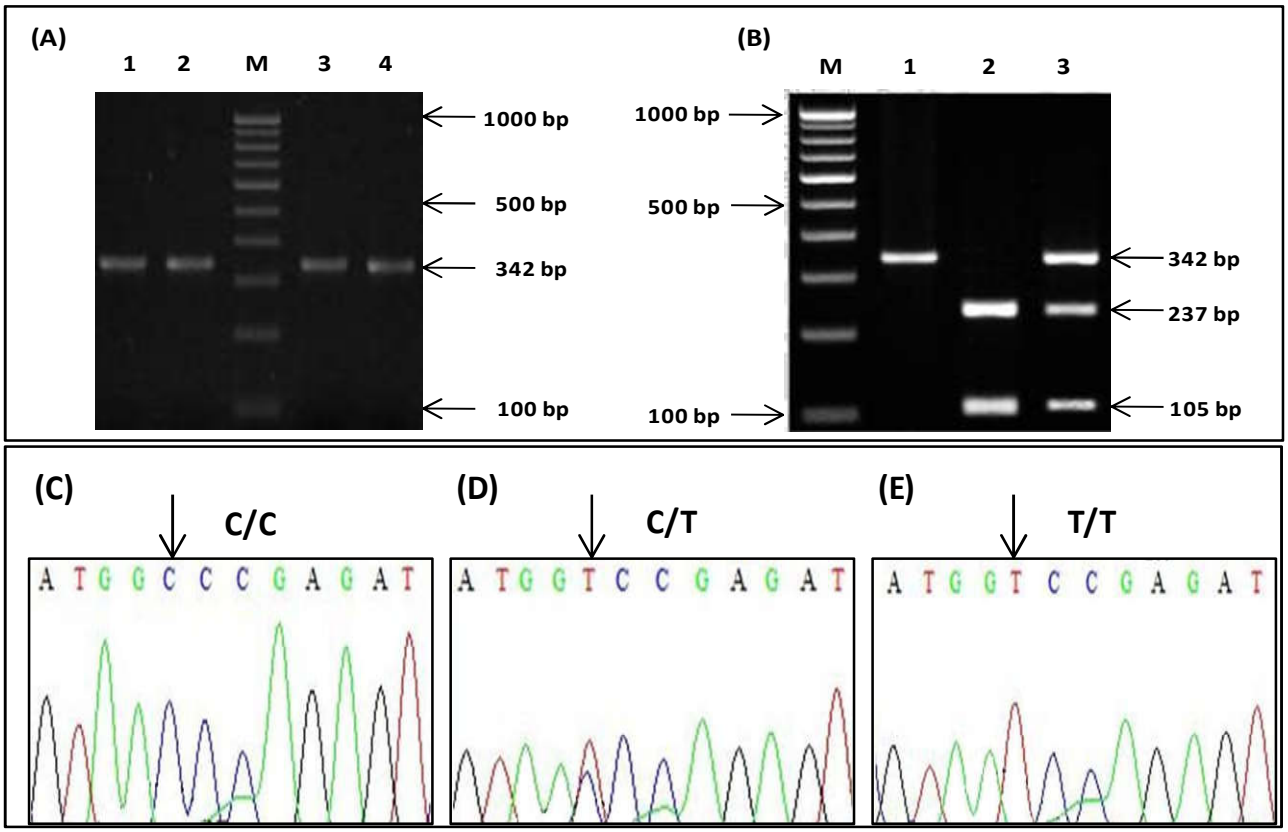

Fig. 1. C/T polymorphism of *CDH13* (*rs7200009*) gene: (A) PCR amplification showing 342bp fragment (Lanes 1-4) [M = 100 bp DNA marker]. (B) *HaeIII*digestion of PCR amplified products for genotyping (Lanes 1 – TT, 2 – CC, 3 – CT). Sequence chromatograms of the genotypes: (C) Homozygous wild-type (CC); (D) Heterozygous (CT); (E) Homozygous variant (TT)

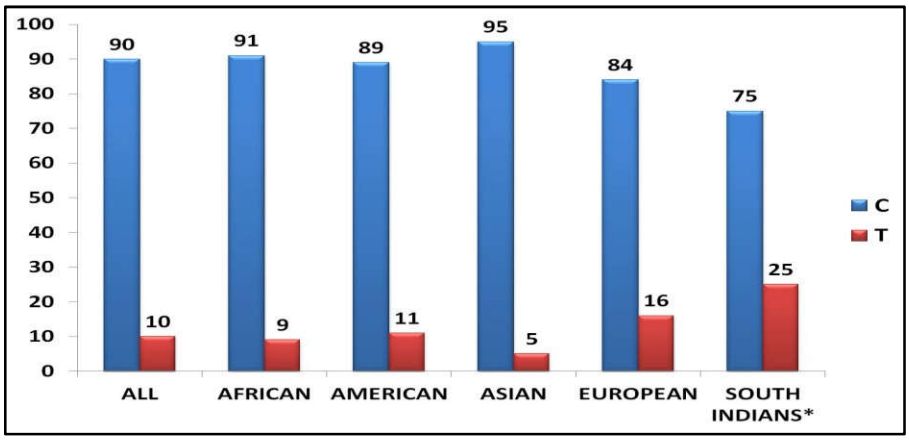

Fig.2. Ethnic distribution of allele frequencies among different populations with the present study group*

Table 1. Mean, standard deviation (SD), blood pressure and BMI of cases and controls

	CONTROLS (N=604)		PATIENTS (N=568)	
Sex (M:F)	1: 1.06		1.08: 1	
Age (Years)				
Males				
Mean + SD	54.4 ± 12.10		54.5 ± 11.27	
Range	21-82		21-82	
Females				
Mean + SD	54.4 ± 12.87		54.5 ± 11.55	
Range	21-82		20-82	
Systolic blood pressure (SBP) mmHg				
Mean + SD	116.8 ± 7.54		154.0 ± 19.93*	
Range	70 - 130		110 - 220	
Diastolic blood pressure (DBP) mmHg				
Mean + SD	77.9 ± 4.69		94.7 ± 12.36*	
Range	60-85		60-150	
Body Mass Index (BMI) (kg/m^2)	**N**	**%**	**N**	**%**
	293		**295**	
Males (N)				
Underweight	16	5.46	24	8.14
Normal	177	60.41	143	48.47*
Overweight	87	29.69	103	34.92*
Obese	13	4.44	25	8.47*
	N	**%**	**N**	**%**
Females (N)	**311**		**273**	
Underweight	31	9.97	20	7.32*
Normal	180	57.88	129	47.25*
Overweight	87	27.97	100	36.64*
Obese	13	4.18	24	8.79*

*p value < 0.001

Table 2. Genotype frequencies of *CDH13* (*rs7200009*) gene polymorphismamong the cases and controls

Genotypes	CC	CT	TT	HWE p value*
Cases N = 568 (%)	360 (63.4)	115 (20.2)	93 (16.4)	$<10^{-7}$
Controls N = 604 (%)	400 (66.2)	132 (21.9)	72 (11.9)	$<10^{-7}$

For departure from Hardy-Weinberg equilibrium (HWE), chi square with one degree of freedom. The genotype frequency of cases and controls do not differ significantly χ_{2df} (P = 0.088).

Table 3. Overall genotype distribution of the *CDH13* gene polymorphism (*rs7200009*) in cases and controls

Models	Cases N=568 (%)	Controls N=604 (%)	Unadjusted OR [95% CI]	P-Value	Adjusted OR* [95% CI]	P-value
Dominant						
CC	360 (63.4)	400 (66.2)	0.883 [0.6944 - 1.1221]	0.308	0.893 [0.701 – 1.136]	0.356
CT + TT	208 (36.6)	204 (33.8)				
Recessive						
TT	93 (16.4)	72 (11.9)	1.447 [1.0384 - 2.0155]	**0.029**	1.427 [1.022 – 1.991]	**0.037**
CT + CC	475 (83.6)	532 (88.1)				
Additive						
C	835 (73.5)	932 (77.2)	0.822 [0.6806 - 0.9916]	**0.041**	-	-
T	301(26.5)	276 (22.8)				

*Odds ratio according to genotypes were estimated after adjusting the confounding variables for BMI.

Table 4. Gender specific distribution of *CDH13* (*rs7200009*) gene polymorphism in male subjects

Models	Cases N=295 (%)	Controls N=293 (%)	Unadjusted OR [95% CI]	P-Value	Adjusted OR* [95% CI]	P-value
Dominant						
CC	187 (63.4)	197 (67.2)	0.844 [0.6005 - 1.1855]	0.328	0.853 [0.606 – 1.201]	0.363
CT + TT	108 (36.6)	96 (32.8)				
Recessive						
TT	42 (14.2)	33 (11.3)	1.308 [0.8031 - 2.1300]	0.281	1.289 [0.789 – 2.106]	0.311
CT + CC	253 (85.8)	260 (88.7)				
Additive						
C	440 (74.6)	457 (78.0)	0.828 [0.6325 - 1.0839]	0.169	-	-
T	150 (25.4)	129 (22.0)				

*Odds ratio according to genotypes were estimated after adjusting the confounding variables for BMI.

Table 5. Gender specific distribution of *CDH13* (*rs7200009*) gene polymorphism in female subjects

Models	Cases N=273 (%)	Controls N=311 (%)	Unadjusted OR [95% CI]	P-Value	Adjusted OR* [95% CI]	P-value
Dominant						
CC	173 (63.4)	203 (65.3)	0.920 [0.6556 - 1.2922]	0.632	0.927 [0.658 – 1.305]	0.663
CT + TT	100 (36.6)	108 (34.7)				
Recessive						
TT	51 (18.7)	39 (12.5)	1.602 [1.0185 - 2.5205]	**0.041**	1.550 [0.981 – 2.450]	0.061
CT + CC	222 (81.3)	272 (87.5)				
Additive						
C	395 (72.3)	474 (76.2)	0.817 [0.6278 - 1.0626]	0.132	-	-
T	151 (27.7)	148 (23.8)				

*Odds ratio according to genotypes were estimated after adjusting the confounding variables for BMI.

In addition to the above data, analysis of genotypic frequencies based on suitable models revealed a significant difference between case and control groups with respect to the TT genotype (p value = 0.029, OR = 1.447, 95% CI = 1.0384 – 2.0155) (Table 3). The significance was lowered on adjusting for BMI (p = 0.037, OR = 1.427, 95% CI = 1.022 – 1.991) (Table 3). From the odds ratio obtained, it was evident that the TT genotype could be the risk genotype for this polymorphism. In the additive model C versus T allele showed a significant difference between the case and control groups (p = 0.041, OR = 0.822, 95% CI = 0.6806 - 0.9916). The distribution of genotype frequencies did not differ significantly between case and control groups of male (Table 4) subjects. While, it showed a significant difference in the recessive model among female subjects (p = 0.041, OR = 1.602, 95% CI = 1.0185 - 2.5205) (Table 5). The results obtained showed that TT homozygous genotype is a risk factor for EH in female subjects. Although significant result was obtained with certain models, higher deviation recorded in the Hardy-Weinberg equilibrium, demands further studies to prove their association.

DISCUSSION

CDH13 gene codes for an adhesion glycoprotein T-cadherin that is a regulator of vascular wall remodeling and angiogenesis (Rubina *et al.,* 2007). Abundant expression of T-cadherin in the myocardium and its association with cholesterol rich membrane domains of the cardiac sarcolemma has raised interest in analyzing their genetic background in relation to blood pressure regulation (Doyle *et al.,* 1998). T-cadherin is also identified as a receptor for adiponectin (APN),a hormone with beneficial metabolic and cardiovascular properties (Shibata *et al.,* 2009). Studies have shown that low APN serum levels correlate with development of cerebrovascular disease (Chen *et al.,* 2005), coronary artery disease (Kumada *et al.,* 2003), myocardial infarction (Hong *et al.,* 2004), hypertension (Iwashima *et al.,* 2004), left ventricular hypertrophy and other cardiovascular dysfunctions. All these features indicate that this gene as a promising candidate for blood pressure regulation. Multiple SNP markers of *CDH13* (cadherin 13) gene has been found to be in strong association with essential hypertension in European and African-American population (Adeyemo *et al.,* 2009; Org *et al.,* 2009; Kidambi *et al.,* 2012). Kooperative Gesundheitsforschung in der Region Augsburg (KORA) S3 cohort performed a GWAS in the general population recruited from Southern Germany. The study showed significant association of *CDH13* gene with all three BP traits: SBP, DBP and hypertension. The results were further replicated in two other European population based cohorts: KORA S4 (Germans) and HYPEST (Estonians) (Org *et al.,* 2009).

The SNP markers *rs7200009* ($p = 1.08 \times 10^{-3}$) and *rs11860907* ($p = 5.71 \times 10^{-4}$) showed a significant association with systolic blood pressure, whereas markers *rs16960421* ($p = 1.82 \times 10^{-3}$) and *rs17177428* ($p = 3.42 \times 10^{-3}$) produced a significant association with diastolic blood pressure in African American population. Kidambi *et al.* (2012) performed a replication analysis on the SNPs identified earlier by Adeyemo *et al.* (2009). The study included an independent population of African American subjects (n=2474) from the mid-western United States. Although the four markers, *rs7200009, rs11860907, rs16960421* and *rs17177428* of *CDH13* gene showed no association with blood pressure, however, borderline associations were identified without statistical adjustments for multiple comparisons. SNP *rs7200009* was associated with both systolic and diastolic blood pressure (p = 0.04) and SNP *rs17177428* was associated with systolic blood pressure (p = 0.04) alone. The result of the present study is in compliance with the result obtained from earlier studies. The TT genotype was found to be the high risk genotype which is evident from the recessive model comparison of TT vs CT+CC between case and control groups (p = 0.029; OR = 1.447). The significance remained the same after adjusting for BMI (p = 0.037; OR = 1.427). The additive model which compared the C vs T allele frequencies between case and control groups revealed the fact that C allele was protective with an odds ratio of 0.822 (p = 0.041). A significant association was also found for the TT genotype after adjusting for BMI (p = 0.041) in female subjects. Whereas, the significance declined after adjusting for BMI in female subjects (p = 0.061). Thus the TT genotype carries risk in female subjects while no such association was observed in the male subjects.

Conclusion

Essential hypertension is complex disease affecting a large proportion of adult population. The scientific and technical resources available have enabled researchers to systematically pursue the identification of gene variation that causes heritable

susceptibility to hypertension. Several genomic surveys have already revealed a substantial divergence in allele frequency, linkage disequilibrium and haplotype structure across populations. Both genetic and environmental influences contribute to the heterogeneity of complex traits. In this context, population based studies would not only provide a clue on the effect of these putative genetic variants but also facilitate the identification of novel variants with more pronounced effect on BP regulation. The variant selected for the present study is an intronic polymorphism. Although introns, the non-coding sequence of the gene have little functional significance, they may influence the level of gene expression by interfering with the splicing mechanisms. They can affect many splicing regulatory elements leading to aberrant splicing. Intronic splicing enhancers (ISE) and intronic splicing silencers (ISS) allow specific splice sites to be distinguished from many cryptic splice sites that have same signal sequences. Genetic variants may also introduce or erase splice sites. Intronic variants may be located ~50bp from the splice sites or deep in the introns. Hence, the association of the variant studied might be a crucial factor involved directly or indirectly in the pathogenesis of hypertension.

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