

## Association of ACE DD genotype with Hypertension among the tribal populations of South India.

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**Abstract** The Renin-Angiotensin System (RAS) is an important regulator of the blood pressure (BP). The level of the vasoactive peptide Angiotensin-II, is mainly determined by the RAS enzyme, angiotensin converting enzyme-1 (ACE-1). Polymorphisms in ACE gene is reported to be associated with hypertension in various populations worldwide. We investigated the association of ACE I/D polymorphisms with hypertension among the tribal populations of South India. Samples were collected from hypertensive patients (n = 33) and healthy controls (n = 37). Genotyping was performed using Polymerase chain reaction (PCR) with allele specific primers. The DD genotype is significantly observed among the cases (OR = 1.0). Specifically, the DD genotype is more evident among the females (OR = 0.705) than males (OR = 1.22) and is analysed to be associated with hypertension among the tribal populations of South India.

### Introduction

The Indian population has been an enigmatic subject for archaeologists, historians, anthropologists and geneticists for many decades, by virtue of its enormous linguistic, historic and cultural diversity [1]. The dominant and most powerful key cultural factor of the Indian subcontinent is the caste system. Dating back to time immemorial, this system is characterized by its well stratified, endogamous and close-cultural values, which could strongly prohibit any exchange from outside. Genetically, this restriction significantly controls the gene flow between the population subgroups, which creates specific genetic patterns, that could make the groups either susceptible or resistant to various diseases [2-3].

Numerous studies were reported at the context of disease epidemiology and genetics, upon various Indian tribal communities, who are highly isolated both demographically and topographically, from the mainstream Indian populations [4-16].

The South Indian tribal communities represent a primitive, negroid, proto-australoid population ancestry, which are characterized by their unique cultural practices and endogamy [17-21].

The angiotensin-I converting enzyme (ACE) gene is widely studied for its crucial roles in the Renin-Angiotensin system (RAS) and reported to be associated with Hypertension and other cardio and cerebrovascular diseases [22 - 23]. Many studies showed that polymorphisms of certain genes related to metabolism, including that of ACE, are also associated with the onset and development of Type 2- Diabetes [22, 24 - 25]. There is a 287 bp DNA fragment insertion (I) and /or deletion (D) polymorphism in the intron 16 of ACE gene [22, 26], which was recently studied [27-31] in the context of its association with Hypertension and Diabetes [22, 28 - 30, 32-35] in various populations worldwide. In this study, we examined the distribution of ACE I/D polymorphisms in their association with Hypertension among the tribal populations of Southern India.

### Subjects and methods:

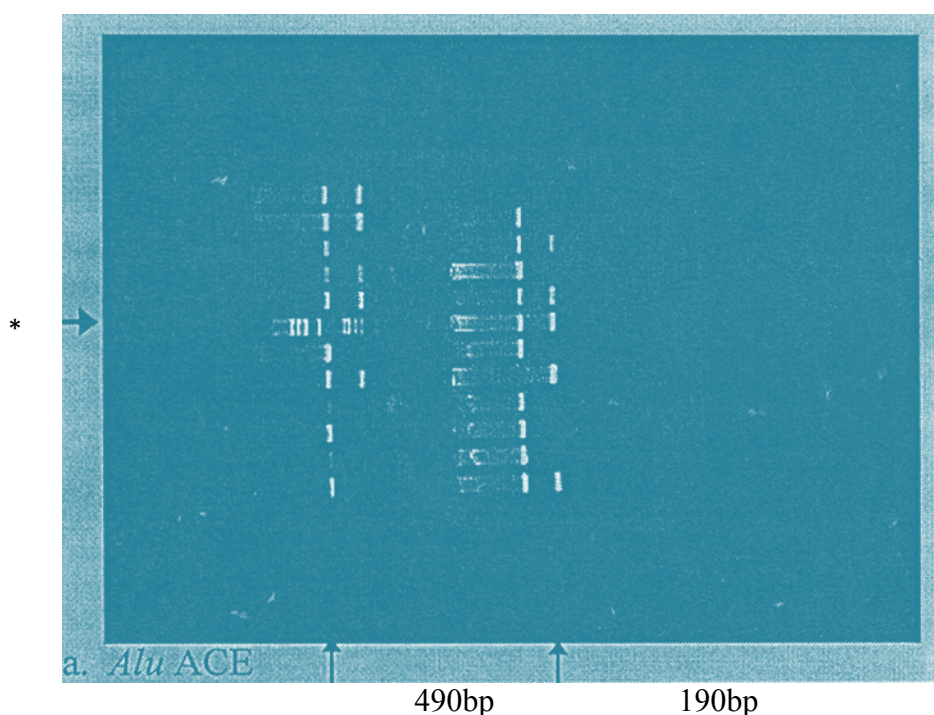
A total of 33 hypertensive patients and 37 healthy controls were included in this study, with blood pressure (BP) measured with standard mercury manometer. Subjects with BP 120/80 mmHg (SBP/DBP) were considered normal, and those with higher values (SBP  $\geq$  140 mmHg and DBP  $\geq$  90mmHg) were considered hypertensive. The selected tribal communities are Mudhuvar, Pulaiyan, Mannan and Kaniyan. Blood samples (5 ml) were collected from the subjects between the age of 15–85 years, with proper informed consents obtained. Genomic DNA was extracted from the whole blood using the Salting out method [ 36 ]. The isolated DNA was suspended and stored in 10mM Tris and 0.1mM EDTA for genotyping. The polymorphic loci were genotyped (**Table: 1**) using the standard 30-cycle PCR. Appropriate annealing temperatures and additives were optimized for each system. The PCR protocols were followed as reported earlier [37- 38]. The amplicons were separated by electrophoresis. Later, the EtBr stained gels were visualized under UV.

### PCR Protocol:

The total volume of the reaction mixture was 20  $\mu$ l, which contained 13.5  $\mu$ l double distilled H<sub>2</sub>O, 2  $\mu$ l 0.5X PCR buffer (Agilent), 0.4  $\mu$ l of 10 mM dNTPs (Genet Bio), 1 $\mu$ l of forward and reverse primers and 0.5  $\mu$ l Taq DNA polymerase (Agilent). PCR cycling conditions were as follows: 1) 95°C for 5 min; 2) 30 cycles of 95°C for 45 sec; 3) 56°C for 30 sec; 4) 72°C for 30 sec and 5) 72°C for 3 min. PCR products were run on 2% agarose gels stained with Ethidium bromide and compared with a 100 base pair DNA ladder under UV illumination (**Fig:1**).

**Table 1: PCR primers and Conditions**

DNA Locus	Chromosome location	Primer sequence	Annealing Tem.°C	Amplified Product size		Agarose gel %
				+	-	
ACE	17q23	F-5'-CTGGAGACCACTCCCATCCTTCT-3' R-5'-GATGTGGCCATCACATTCGTCAGAT-3'	58	490 bp	190 bp	2



**Fig. 1: Gel Patterns of Alu ACE Indels**

**Statistical analysis:**

The software package SPSS 16.0 was used for the analysis of odds ratio (OR), involving both the genotype and allele frequencies. The analyses of allelic associations using the  $\chi^2$  test with P values <0.05 as significant, were performed using the population genetics package, POPGENE [39]

**Results:****Table 2: Distribution of allele frequencies in Cases and Controls stratified according to gender.**

SNP	Gender	Minor allele	Freq. allele case	Freq. allele control	Case (n= 33)	Control (n= 37)	$\chi^2$	OR	95% CI	P-value
ACE I/D	All	I	0.29	0.64	33	37	13.39	1.0	0.616 – 1.602	0.0135
	Female		0.38	0.68	20	20	10.03	0.65	0.323 – 1.307	1.484
	Male		0.23	0.61	13	17	5.16	1.715	0.616 – 2.25	0.108

$\chi^2$  : Chi-square with 1 degree of freedom; OR: odds ratio

**Table 3: Distribution of genotype frequencies of polymorphisms in Patients and Controls.**

SNP	Gender	Genotype	Case% (n= 33)	Control% (n = 37)	OR	95% CI	P-value
ACE I/D	All	II	21.2 (7)	59.5 (22)	Ref		
		ID	15.15 (5)	8.1 (3)	0.666	0.414 3.989	0.2
		DD	63.6 (21)	32.4 (12)	1.0	0.449 2.225	0.0417*
	Female	II	30 (6)	65 (13)	Ref		
		ID	15 (3)	5 (1)	1.70	2.26 127.74	12.5
		DD	55 (11)	30 (6)	1.5	0.534 4.214	0.267
	Male	II	13.4 (2)	53 (9)	Ref		
		ID	13.4 (2)	12 (2)	0.55	1.219 24.814	6.231
		DD	69 (9)	35(6)	0.667	0.19 2.36	0.1

\* Statistically significant. n: Sample size; OR: Odds ratio; CI: Confidence Interval; Ref: References.

**Table 4: Distribution of ACE I/D polymorphisms (dominant and recessive model) in Patients and Controls.**

SNP	Gender	Model	TEST	Case (n= 33)	Control (n= 37)	OR	95% CI	P-value
ACE I/D	All	II+ID Vs DD	DOM	12/21	25/12	0.84	0.470 1.5	0.1957
		II Vs ID +DD	REC	7/25	22/15	1.136	0.641 2.015	0.085
	Female	II+ID Vs DD	DOM	9/11	14/6	1.5	0.534 4.214	0.267
		II Vs ID +DD	REC	6/14	13/7	0.785	0.365 1.73	0.00*
	Male	II+ID Vs DD	DOM	4/9	9/6	1.0	0.3992.51	0.06
		II Vs ID +DD	REC	2/11	9/8	1.222	0.507 1.95	0.05*

DOM: Dominant model; REC: Recessive model; n: sample size; OR: Odds ratio; CI: Confidence Interval; DOM model: Only when DD is present, the diseases would be caused, REC model: when D is in homozygous or heterozygous it will cause diseases.

\* Statistically significant.

Association studies between genetic polymorphisms and diseases are the hallmarks for unravelling the genetic pattern of complex diseases. Studying the relationship between allelic and genotype frequencies of candidate genes among both affected and healthy subjects, to understand the genetic etiology of complex human traits, is an efficient method to elucidate their disease pathogenesis.

Henceforth, we tried to elucidate the possible association of the ACE I/D polymorphisms with Hypertension among the tribal communities of South India. The D allele was observed to be more prevalent among cases than controls, as shown in **Table 2 and 3**. Genotype distributions, allelic frequencies and the corresponding odds ratios (OR) were calculated for each variant as shown in **Table: 4**.

No significant association was observed in the ungrouped data. However, when segregated the subjects into male and female, we found that the DD homozygous genotype has a significant prevalence upon females than in males. An increase in the frequency of DD (63.6%) homozygous genotype was observed among the patients than controls (32.4%) (**Table:3**). As shown in **Table: 4**, the distribution of the DD genotype is more dominant, when compared to the ID and II genotypes.

### Discussion:

The gene encoding angiotensin converting enzyme (ACE) of RAS is polymorphic and frequently reported to be associated with Hypertension[40]. Epidemiological studies show that various genetic and environmental factors are involved in the pathogenesis of Hypertension. ACE is the key enzyme in the Renin-Angiotensin system, which can catalyze the conversion of Angiotensin-I to Angiotensin-II [22,24,41]. The ACE gene is located in chromosome 17q23 and contains 26 exons and 25 introns with a total length of 21 kb. The Insertion/Deletion (I/D) polymorphisms are defined according to presence or absence of the 287 bp fragment in intron 16.

Alu elements are mobile genetic elements [42], deriving their name from the Alu I restriction sites they comprise [43]. ACE gene is one of the insertional polymorphisms of Alu elements [44-45]. Many reports studied the Alu polymorphisms in the context of human genetics and evolution [46-53].

Recently, various studies reported the relationship between ACE gene polymorphism and Type 2 Diabetes. For example, the recently published meta-analysis [51], comprising a total of 41 studies with 4708 cases and 5368 controls, analyzed the association between ACE I/D polymorphisms and Type 2-Diabetes in Chinese population. Another report on Egyptian populations suggests that the DD genotype and the D allele are associated with hypertension and Type 2 Diabetes[55]. The exact role of ACE gene in the onset of hypertension remains controversial. Woo et al, [56] reported that the ACE gene is not associated with hypertension. However, in other population-based studies, the D allele was found to be associated [56-58].

The present study revealed the association of ACE genotypes with hypertension among the tribal population (n = 70) of the Southern region of India. In contrast to the urban populations, these tribal populations represent a genetically homogenous primitive population subgroups, where the former is highly heterogenous in nature. Hence, studies with these demographically isolated communities could yield valuable results in the field of medical genetics and history and anthropology. In this study, we utilized the common Case-control design to analyze these associations. The DD homozygous genotype is found to be associated with hypertension. The same ACE DD genotype is also reported to be associated with diabetic nephropathy in north Indian populations [59].

Since, the genetic matrix is a non-modifiable factor in the causation of diseases, greater attention should be given to modify the environmental factors. The clinicians could identify groups of patients, with the susceptible ACE genotypes that need intensive monitoring and correct the risk factors such as smoking, alcohol consumption and high BMI for an effective prevention of both onset and the development of hypertension.

## Conclusion

In conclusion, a significant association of the DD genotype with hypertensive patients, especially, with females of the tribal populations was observed. With the observed association of II/DD genotype with hypertension, this study anticipates more studies with larger cohorts to extend and elucidate these associations.

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