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Role of Insertion/deletion polymorphism of ACE gene in hypertension in Vindhyan region

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Abstract
Hypertension is a term related to high blood pressure and it referred to the condition that affects almost one billion people worldwide, and it is a leading cause of morbidity and mortality. Renin angiotensin system (RAS) plays an important role in the regulation of blood pressure. Association between candidate gene polymorphisms of RAS and EH has been reported in different populations. A PCR based I/D polymorphism study in central Indian patients were perform to detect ACE polymorphism and its pathophysiological role in hypertension. Overall genotype pattern of ACE ID gene was significantly different between case and control (χ^2 =6.593, d.f. =2, P value= 0.0370). The pattern of genotype and allele distribution in disease and control group suggested association of ACE I/D in Hypertension susceptibility.
Keywords: Hypertention, RAS, Vindhya region

Introduction
Hypertension is a term related to high blood pressure and it referred to the condition that affects almost one billion people worldwide, and it is a leading cause of morbidity and mortality. More than 20% of Americans are hypertensive, and one-third of Americans are not even aware that they are hypertensive. Therefore, the disease is sometimes called as "silent killer". This disease is usually asymptomatic until its damaging effects of hypertension (such a stroke, myocardial infarction, renal dysfunction, visual problems, etc.) are observed. Major risk factor for coronary artery disease, myocardial infarction ("heart attacks") and stroke is Hypertension. RAS plays a crucial role in the initiation and maintenance of vascular inflammation and vascular remodeling. Vascular inflammation leads to endothelium dysfunction. A dysfunctional endothelium is leaky and facilitates migration of inflammatory cell into the vascular wall and stimulates smooth muscle cells proliferation. The renin-angiotensin system (RAS) plays a central role in the regulation of sodium metabolism, vascular tone, blood pressure, renal haemodynamics, and vascular modelling.

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Genetic variants of its major components such as the insertion/deletion polymorphisms of angiotensin converting enzyme I (*ACE-I/D* have been implicated in the pathogenesis of hypertension, cardiovascular and renal diseases (Miller and Scholey, 2004).

Material and Methods
Study population
The study population consisted of 440 unrelated subjects and comprised 210 hypertension patients and 230 ethnically matched healthy controls of Indo-European ethnicity. Cases included consecutive patients who attended the Department of Medicine at Shyam Shah Medical College, Rewa, India; Ayurveda Medical College, Rewa, India; Ranbaxy Pathology Regional Collection Centre, Rewa, India; and the District Hospital, Satna, India.

DNA isolation
Genomic DNA was extracted from whole blood using a modified version of the salting-out procedure described by Miller et al.

PCR Amplification
Isolated DNA is amplified with specific primers (Ramu et al.,2011)
5'-CTGGAGAGCCACTCCCATCCTTTCT-3' (Forward)
5'-GACGTGGCCATCACATTCGTCAGAT-3' (Reverse).
The PCR products were run on 2% agarose gel electrophoresis. The different fragments obtained were 490bp II, 190bp DD, and 490bp and 190bp ID.

Results and Discussion

Overall genotype pattern of ACE ID gene was significantly different between case and control (χ^2 =6.593, d.f. =2, P value= 0.0370). Hypertension group showed increase in 'I/I' genotype as compared to control group (38.7% vs *30.5*%) but was significantly different. Genotype 'D/D' was significantly higher in HC group as compared to Hypertension group (16.5% vs. 25.7%). An odds ratio of 1.749 (1.098-2.787). An odds ratio of 0.6945 of common 'I/I' genotype group respectively was consistent with little or no effect of this genotype in Hypertension susceptibility. The heterozygous genotype 'I/D' was significantly distributed in HC group as compared to Hypertension group (44.8% vs 43.8%). An odds ratio of 0.9613 of 'I/D' showed weak protective or no association in Hypertension susceptibility.

Overall allele distribution was also significant but less common 'D' allele was found in higher frequency in control as compare to Hypertension patients (47.6% vs 38.9%) and 'I' allele was found at higher frequency in case as compare to control (61.1%vs 52.4%) but the difference was significant (χ^2 =6.787 P= 0.0092). Carriage rate of allele 'I' was equivalent to HC group and Hypertension group. Whereas carriage rate of allele 'D' was higher in control group (61.3% vs. 69.5%) but not significantly different between case and control (χ^2=2.303 P=0.1291) odds ratio of minor allele 'D' was 1.427 which clearly indicates its little or moderate protective effect of minor allele "I" in our population meanwhile odds ratio of 0.7007 for Major allele 'I' showed its little association with Hypertension susceptibility but overall significance was seen. The pattern of genotype and allele distribution in disease and control group suggested association of ACE I/D in Hypertension susceptibility.

Blood pressure (BP) is a highly quantitative trait and therefore it has been difficult and somewhat arbitrary to define specific levels at which high blood pressure becomes too high, i.e. hypertension. As there is a strong correlation between cardiovascular, renal complications and hypertension, a practical definition and classification of high blood pressure to assess patients and provide treatment has been agreed upon and revised (Carretero & Oparil 2000). Overall allele distribution was also significant but less common 'D' allele was found in higher frequency in control as compare to Hypertension patients (47.6% vs 38.9%) and 'I' allele was found at higher frequency in case as compare to control (61.1%vs 52.4%) but the difference was significant (χ^2 =6.787 P= 0.0092). Carriage rate of allele 'I' was equivalent to HC group and Hypertension group. Whereas carriage rate of allele 'D' was higher in control group (61.3% vs. 69.5%) but not significantly different between case and control (χ^2=2.303 P=0.1291) odds ratio of minor allele 'D' was 1.427 which clearly indicates its little or moderate effect of minor allele "I" in our population meanwhile odds ratio of 0.7007 for Major allele 'I' showed its little protective effect on Hypertension susceptibility. The pattern of genotype and allele distribution in disease and control group suggested association of ACE I/D in Hypertension susceptibility. Previous studies already done in india shown ACE ID gene polymorphism in the Indian population showed a significant association with DD genotype and diastolic blood pressure in men (Bhavani et al. 2004), but other one study did not show such association with DD genotype in hypertensive men (Ashavaid et al. 2000). However, our results are similar with the Japanese (Higaki et al. 2000), Indians (Bhavani et al. 2005), Turkish study (Agachan et al. 2003), African-Americans (Duru et al. 1994) and Framingham heart study (O'Donnell et al. 1998).

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Fisher's Exact Test table of ACE I/D Polymorphism

Genotype	Case - 210 N	%	Control 230 N	%	P Value	Odds Ratio & (CI)
I/I	64	30.5%	89	83.5%	0.0724	0.6945 (0.4674-1.032)
I/D	92	43.8%	103	44.8%	0.8482	0.9613 (0.6596-1.401)
D/D	54	25.7%	38	16.5%	0.0192	1.749 (1.098-2.787)
Allele Frequency I	220	52.4%	281	61.1%	0.0097	0.7007 (0.5360-0.9161)
D	200	47.6%	179	38.9%	"	1.427 (1.092-1.866)
Carriage Rate I	156	74.3%	192	83.5%	0.1304	0.7847 (0.5735-1.074)
D	146	69.5%	38	61.3%	"	1.274 (0.9315-1.744)

***denotes the level of significant association between case and control.**
N - Number of individuals in study group.
% - Genotype allele frequency and carriage rate expressed in percentage.

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