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Research Article

Ace Gene Polymorphism Insertion Deletion Association with Prostate Cancer

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ABSTRACT
The angiotensin-converting enzyme (ACE) gene carries two alleles: insertion (I) and deletion (D) polymorphism inside its intron 16 . The study investigation the association between genetic polymorphisms and prostate patients. Materials and Methods: 75 prostate cancer patients, 75 prostate benign and 81 healthy were included. The ACE I/D genotypes were determined by PCR (polymerase chain reaction) Results showed for ACE gene polymorphism at that DD allele relation with prostate cancer p-value 0.0001** and prostate benign relation with ID allele p-value 0.0097**. This study aimed to detecting genetic early marker in angiotensin I converting enzyme (ACE) gene Iraqi patients with prostate carcinoma.

Keywords: polymorphism, prostrate cancer.

INTRODUCTION

Prostate cancer is the development of cancer in the prostate (a gland in the male reproductive system). Most prostate cancers are slow growing; however, some grow relatively quickly[1]. The cancer cells may spread from the prostate to other parts of the body, particularly the bones and lymph nodes. It may initially cause no symptoms. In later stages it can lead to difficulty urinating, blood in the urine, or pain in the pelvis, back or when urinating. A disease known as benign prostatic hyperplasia may produce similar symptoms. Other late symptoms may include feeling tired due to low levels of red blood cells[2]. Researchers estimate that prostate cancer accounted for 27,540 deaths in 2016 in world. In UK, the number of new cases of prostate cancer was 119.8 per 100,000 men per year. The number of deaths was 20.1 per 100,000 men per year[3]. In Iraq prostate cancer ranks the 10th among leading cancers in male There is 473 new cases which constitute 2.78 per/ 105 in 2015[4].

Prostate cancer has a complex, multi-factorial etiology with an estimated 45% of disease variation being attributed to genetic factors and 50% to environmental/lifestyle factors[5]. Factors that increase the risk of prostate cancer include older age, a family history of the disease. The greatest risk factor for prostate cancer is age. About two-thirds of all prostate cancers are diagnosed in men age 65 and older. The older the patient, especially if they are over 70 years old[6]. Understanding geographical patterns of prostate cancer incidence and mortality is important in order to detect any disparities in access to diagnostic and treatment services. In particular, the physical distances to access specialist services are believed to disadvantage rural patients. A change in the human ACE gene occurs by an insertion (I) or a deletion (D) in intron 16, leading to a change in the plasma ACE level. This ACE I/D polymorphism genotypes and changed levels of circulating and tissue ACE activity lead to increasing the incidence of prostate cancer[7].

MATERIALS AND METHODS

The study involved 231collected samples of blood from men, who were distributed into three groups of malignant, benign and a pearmently healthy. Malignant tumor group included 75 patients whose age range was between 60 - 75 years (68.03 ± 5.73 year), while benign group that included 75 patient's range of age was between 45- 65 years (56.42 ± 3.95 year) and apparently health men were 81 individuals that enrolled in this study, their age range was 25-65 year (49.28 ± 6.10 year).

The patients were referred to the Middle Euphrates cancer center in AL-Najaf during the period from December 2015 – August 2016.All samples were diagnosis by specialist physician as a prostate tumor male that treated with anticancer therapy. Furthermore, the patients were also followed-up after the surgical operation to define the histopathological classification of prostate tumor.

DNA isolation. Blood samples were collected in tubes containing EDTA (ethylene diamine tetra acetic acid)[16]. ACE I/D polymorphism. The template DNA (0.5-1.0 Ìg) was used in a PCR (polymerase chain reaction) under stringent conditions to avoid the possibility of false positives for ACE genotyping. Genomic DNA was extracted from whole blood using Promega Kit (Company, USA). PCR was carried out according to the method of Rigat B). The sequences of the forward and reverse primers were: 5'-CTG GAG ACC ACT CCC

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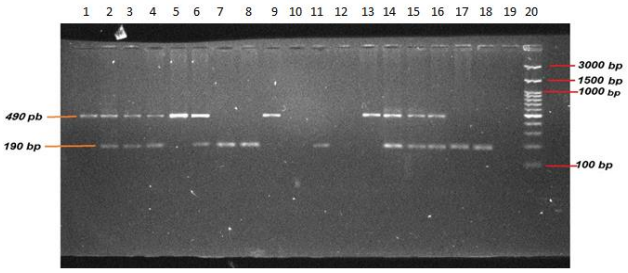

Figure 1: PCR products of *ACE* gene – intron 16 (benign) of the molecular size 490bp and 190 for alleles (I, D) indicated by red arrow. Bands were separated by electrophoresis on 2 % agarose gel at 90 voltages for one hour and visualized by gel documentation system after 30 minutes of staining with EtBr
Lane: 1, 5,9,13 insertion allele (II)
Lane: 7, 8,11,17,18 deletion (DD)
Lane: 2, 3, 4, 6,14,15,16 insertion / deletion (DI)
Lane: 20 DNA marker with 100 – 3000 pb ladder

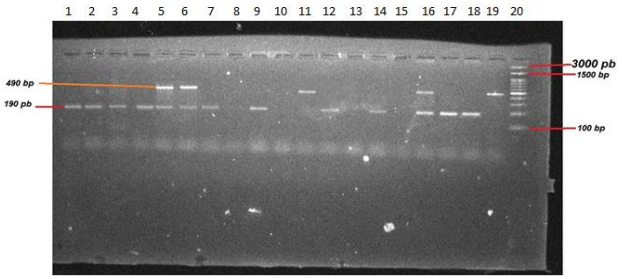

Figure 2: PCR products of *ACE* gene – intron 16 (Malignant) of the molecular size 490bp and 190 for tow alleles (I, D) indicated by red arrow. Bands were separated by electrophoresis on 2 % agarose gel at 90 voltages for one hour and visualized by gel documentation system after 30 minutes of staining with EtBr
Lane: 11, 19 insertion allele (II)
Lane: 1,2,3,4, 7, 9, 12, 14, 16, 17 deletion (DD)
Lane: 11, 19 insertion / deletion (DI)
Lane: 20 DNA marker with 100 – 3000 pb ladder

Table 1: The percentage of polymorphism of ACE gene in prostate cancer patients.

The group	Total No.	II	ID	DD	Chi-square	O.R.
Controls	81	36 (44.44%)	18 (22.22%)	27 (33.33%)	8.944 **	1.307
Benign	75	20 (26.67%)	35 (46.67%)	20 (26.67%)	8.615 **	1.052
Malignant	75	10 (13.33%)	20 (26.66%)	45 (60.00%)	11.374 **	1.766
P-value	---	0.0001 **	0.0027 **	0.00018**	---	---
O.R.	---	1.759	1.241	1.658	---	---

** (P<0.01).

Table 2: Allele frequency (Allele I and D) in different genotype groups.

Allele	Allele frequency		
	Controls	Benign	Patients
I	0.56	0.50	0.27
D	0.44	0.50	0.73

ATC CTT TCT-3' and 5'-GAT GTG GCC ATC ACA TTC GTC AGA T-3', respectively[8].

RESULTS AND DISCUSSION

The result of gel electrophoresis for PCR product of ACE gene illustrated three different genotype, one in homozygote deletion in a region of ACE gene (DD) represented in band 190 pb, second genotype is homozygous insertion (II) represented in molecular size of band 490 bp, furthermore a third heterozygous genotype (ID) represented a band 190 bp, 490 bp. This study has shown that the DD genotype is over-represented in prostate cancer and shows the detrimental effect of the D allele (p=0.00018). The DD genotype is significantly associated with advanced disease. ACE I/D polymorphism is also associated with high BTPSA levels, lymph node metastasis and tumor development. The DD genotype has been shown to be associated with high ACE levels, leading to angiogenesis and this angiogenesis could cause detrimental effects leading to lymph node metastasis. Based on all the studies on the ACE I/D genotype and circulating ACE levels, the use of ACE inhibitors may reduce the proliferation of tumor cells and tumor growth in prostate cancer[9].

It is clear from the obtained results that individuals who carry D allele are proportional to their direct presence with prostate cancer p-value (0.0001) and individuals who are benign to the allele ID a non-homogeneous form, with a significant difference in the percentage of people who suffer from benign enlargement of the prostate p-value (0.0097) and the results showed higher significance in in percentage the allele II (p-value < 0.01) in apparently healthy control.

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