RESEARCH COMMUNICATION

MTHFR Gene Polymorphisms in Bladder Cancer in the Turkish Population

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Abstract

Bladder cancer is the 9th most common cancer and is responsible for malignancy related death all on the world. Folate and folate related enzyme polymorphisms related to the cancer risk. The methylene tethrahydrofolate reductase (MTHFR) enzyme is folate related and association of bladder cancer and MTHFR gene. Our purpose was to assess the prevalence of MTHFR gene 677 CT and 1298 AC polymorphisms and Bladder cancer in Turkey. We intended that bladder cancer patients and controls and we used the Polymerase Chain Reaction (PCR) and Restriction Fragment Length Polymorphism (RFLP) methods. The MTHFR gene C677T and A1298C polymorphisms were associated with an increased risk of bladder cancer in our population (For the MTHFR gene C677T polymorphism and A1298C polymorphism; p=0.036<0.05; p=0.278>0.05 respectively). Consequently, the MTHFR gene C677T polymorphism augments the risk of bladder cancer in Turkey.

Keywords: Bladder cancer - MTHFR gene - polymorphism

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Introduction

Bladder cancer is cause of cancer death globally and is the 9th most common malignancy. Parkin et al. reveal that bladder cancer appears 357.000 new cases and causes 145.000 death worldwide (Shelley et al. 2002).

Folate plays the key role of supplying methyl groups for deoxynucleoside synthesis in humans (Blount et al. 1997). Duthie et al. has been shown low folate levels association between uracil disincorporation, chromosomal DNA damage, DNA strand breaks, impaired DNA repair and DNA hypomethylation (Duthie et al., 1999). A lot results have been revealed suggesting the role of folate and folate related enzyme polymorphisms in the etiology of cancer (Potter et al., 1993; Steinmetz et al., 1996). Folate related enzymes consist of lots of enzymes which one of them is the methylene tethra hydrofolate reductase (MTHFR) (Friedman et al., 1999; Parle-McDermott et al., 2006). The gene of this enzyme is called MTHFR gene and located on chromosome 1p36.3. Two common polymorphisms in the MTHFR gene are C677T and A1298C. First polymorphism C677T positioned in exon 4 (Goyette et al., 1994) leading to an alanine to valine conversion (Frosst et al., 1995). The other polymorphism A1298C is located in exon 7 and glutamic acid to change alanine.

Previous studies have been shown that folate related to DNA damage causing cancer. Folate metabolism including MTHFR gene and having polymorphisms are affected ethnic backgrounds. Therefore, we designed this study about association of MTHFR gene and Turkish population.

Materials and Methods

Study Population

This study was designed on cases were diagnosed with bladder cancer in urology institute on Cukurova University Medical Faculty Hospitals. 54 cases of having bladder cancer disease (59,85±14,089; 49 male, 6 female) and 50 controls (57,00±10,105; 34 male, 16 female) were recorded into the present study. Control group was composed of not having bladder cancer themselves and relatives. Whole came from the Cukurova region of southern Turkey, whose clinical data were on record at Cukurova University, Faculty of Medicine Hospitals, Adana, Turkey. The obtained bladder tissues were collected (fixed) into % 10 formolin solution and stored at -20°C. The research protocol was approved by the Ethical Committee of Cukurova University, Medical Faculty.

Genotype Assessment

The DNA isolation of the bladder tissues from bladder cancer patients groups the DNA isolation of the tissue samples collected from cases was performed by a

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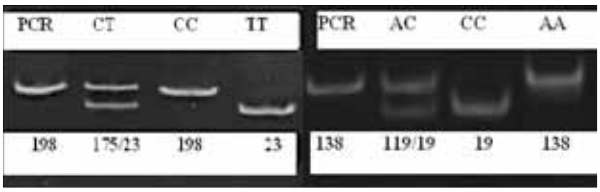

Figure 1. Polyacrylamide Gel Photograph of the MTHFR gene C677T and A1298C Polymorphisms

precipitation method in which a saturated saline solution was used (Miller et al. 1988).

PCR amplification used primers and conditions as described in for the C677T polymorphism. The 198-bp PCR product was digested 3 hours with Hinf I at 37˚C. For the A1298C polymorphism, PCR amplification used primers and conditions as described in (Izmirli et al. 2009). PCR product was 138-bp, being digested with Ita I at 37˚C at 3 hours. Finally, genotypes were assessed on a 10% polyacrylamide gel (Figure 1). According to this; C677T polymorphism CC, CT and TT genotypes were 198-bp, 175/23-bp and 23-bp respectively. The other polymorphism was A1298C; AA, AC and CC genotypes were 138-bp, 119/19-bp and 19-bp respectively.

Statistics

The statistical analysis of data was performed by a SPSS (11.5 version) program. Outcomes were assessed with Pearson Chi-Square test which was utilized to compare ratios and $p<0.05$ was accepted as statistically meaningful.

Results

The genotype frequencies of CC, CT and TT in the bladder cancer patients were 51.9% and 40.7% and 7.4% respectively and for the control group were 72%, 28% and 0% respectively (Table 1). The adjusted p value between the patients and controls for the C677T polymorphism was significant. This shows that there was a meager relation in risk of prostate cancer between cases and controls for the MTHFR gene C677T polymorphism (p=0.036).

AA, AC and CC genotypes frequencies for the A1298C polymorphisms in the MTHFR gene were 40,4%, 53,2% and 6,4% respectively in bladder cancer patients and those of genotypes in the controls were 28%, 58% and 14% respectively. We show that no difference between the patients and controls for A1298C polymorphism (p=0.278).

Discussion

We studied the influence of common MTHFR C677T and A1298C polymorphisms on the risk of bladder cancer in Turkish population. We propose that significant differences between the bladder cancer patients and controls for C677T polymorphism in the MTHFR gene. For the other polymorphism, no association is found with patients and controls.

Some of the previous studies imply that noteworthy difference between patients and controls; in contrast, remaining studies found that no difference for both

Table 1. Genotypes Distribution for MTHFR Gene Polymorphism in Bladder Cancers and Controls

Genotype	Bladder Cancer n(%)	Control n(%)	p value
GC677T Polymorphism			
CC	28 (51.9)	36 (72.0)	0.036
CT	22 (40.7)	14 (28.0)	
TT	4 (7.4)	0 (0.0)	
A1298C Polymorphism			
AA	19 (40.4)	14 (28.0)	0.278
AC	25 (53.2)	29 (58.0)	
CC	3 (6.,4)	7 (14.0)	

of polymorphisms. Certain studies whose outcomes demonstrate that act to increase bladder cancer risk for C677T polymorphism in the MTHFR gene (Heijmans et al., 2003; Sanyal et al., 2003; Lin et al., 2004; Manuguerra, 2007; Cai et al., 2009; Wang et al., 2009). Our findings correlate aforementioned studies. Whereas, some studies found that no association is found between C677T polymorphism and bladder cancer (Sanyal et al., 2004; Karagas et al., 2005; Moore et al., 2007; Rouissi et al. ,2009; Safarinejad et al., 2010; Chung et al., 2010).

Exclusively for two studies declare that their finding was statistically significant for the MTHFR gene A1298C polymorphism (Cai et al., 2009; Safarinejad et al., 2010). However, there are a lots of studies maintain being no differences between bladder cancer patients and controls for A1298C polymorphism (Sanyal et al., 2004; Karagas et al., 2005; Moore et al., 2007; Rouissi et al., 2009). Our outcomes support these results of studies based on MTHFR gene A1298C polymorphism in bladder cancer patients in Turkish population.

Consequently, because of the ethnic background acts genetic polymorphism, there are a lot of studies about different populations. Therefore, we also focus on Turkish populations for MTHFR gene. According to our sample size, MTHFR gene C677T polymorphism correlates with bladder cancer risk. So as to gain a definite result, larger sample size is demanded, for the certain correlation further studies may be overcome. However, our results have important glances for bladder cancer diagnose and so in susceptible populations, the ailment diagnosed before the healthy person have bladder cancer is important for preventive medicine.

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