Methylenetetrahydrofolate Reductase Polymorphisms at Familial Bladder Cancer: Case Report

Ailesel Mesane Kanserlerinde Metilentetrahidrofolat Redüktaz Polimorfizmleri: Olgu Sunumu

MTHFR Polimorfizmi ve Mesane Kanseri / MTHFR Polymorphism and Bladder Cancer

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Özet

Mesane kanseri tüm dünyada erkeklerde en sık görülen 7. kanser türüdür. Türkiye'de ise akciğer kanserinden sonra ikinci, ürogenital tümörler arasında ise birinci sırada görülmektedir. Birçok moleküler epidemiyolojik çalışmada özellikle MTHFR C677T ve A1298C polimorfizmleri ile mesane kanseri arasında ilişki saptanmıştır. Bu vaka sunumunda, transisyonel hücreli mesane kanserine sahip iki kardeşte MTHFR A1298C heterozigositesi saptanmıştır, bu da MTHFR varyantları ve mesane kanseri arasındaki ilişkiyi doğrulamaktadır. Bu bulgu, farklı etnik grupları içeren daha büyük toplulukları içeren prospektif çalışmalarla desteklenebilir.

Anahtar Kelimeler

Ailesel Mesane Kanseri; Polimorfizm; Metilentetrahidrofolat Redüktaz Geni

Abstract

Bladder cancer is the seventh most common cancer in men in the world, it is the second most seen cancer after lung cancer and the first in urogenital tumours in Turkey. Many molecular epidemiologic studies have been reported to investigate the associations between the MTHFR C677T and A1298C polymorphisms and bladder cancer risk. In this report, a family with transitional bladder cancer have also MTHFR A1298C heterozygosity which supports the association between MTHFR variants and bladder cancer. This finding should be further validated by prospective and larger studies with more diverse ethnic groups.

Keywords

Familial Bladder Cancer; Polymorphism; Methylenetetrahydrofolate Reductase Gene

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Introduction

Bladder cancer is the seventh most common cancer in men in the world and the seventeenth in women. According to KIDEM (Cancer Follow-up and Control Center) studies, it is the second most seen cancer after lung cancer and the first in urogenital tumours in Turkey [1]. Bladder cancer usually occurs in 6th and 7th decades. Although the rate of men/women is 3/1, the deaths because of bladder cancer is mostly seen in women (31%) [1]. 90-95% of bladder cancers are transitional cell cancer. Transitional cell bladder cancers are restricted to mucosa and submucosa at the time of diagnosis approximately in 80% of the patients. This is called as non-muscle invasive bladder cancer. 20% of bladder cancer are local forward stage at the time of diagnosis, 20% of them are metastatic. Cigarette smoking is the most important risk factor for bladder cancer, accounting for 50% of cases in men and 35% in women, but the exact mechanism is not yet understood. Cigarette smoke contains some of xenobiotics, including oxidants and free radicals and cigarette smoke exposure was associated with decreased levels of serum and red blood cell folate and vitamin B12 antioxidants [2]. On the other hand, it has been also reported that plasma total homocysteine concentration is higher in smokers than in nonsmokers. According to these findings, the combined effects of smoking with decreased levels of folate and vitamin B12 and an increased level of homocysteine can induce increased chromosomal damage. If it is so, DNA damage induced by smoking may be modulated by the folate metabolic pathway. Folate and methionine metabolism play important roles in DNA synthesis and DNA methylation, their metabolic pathways may affect disease susceptibility. Methylenetetrahydrofolate reductase (MTHFR) and methionine synthase (MS) are two main enzymes involved in the folate metabolism [2]. MTHFR catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, this is the predominant form of folate in plasma and provides the methyl group for de novo methionine synthesis through homocysteine remethylation. The C677T and A1298C are two common polymorphisms in the MTHFR gene affecting enzyme activity. Many molecular epidemiologic studies have been reported to investigate the associations between the MTHFR C677T and A1298C polymorphisms and bladder cancer risk [3]. In this case report, we defined a family with bladder cancer who had MTHFR C677T and A1298C polymorphisms. This study can also be a research for folate metabolic genetic variations on risk of bladder cancer development.

Case Report

A 39-year-old male was admitted to urology clinic because of the complaints of painless clotted hematuria. After the urological examination, he hospitalized for hematuria etiology. A papillary tumor with a diameter of 3cm at the right lateral wall of the bladder was determined in the diagnostic cystoscopy. Tumor was excised. The pathological diagnosis was non-muscle invasive bladder cancer. The patient was followed by control cystoscopies. After 9 months, tumor was detected again in the bladder at the control cystoscopy and it was taken out. The patient's TCC was classified as muscle invasive (Figure 1). Cystectomy and ileal loop operation was performed for the patient. The patient was recovered and discharged in postoperative 10th day. The family of the patient had a bladder cancer story, so he and his family sent to medical genetics department for genetic analysis (Figure 2). Informed consent form of the patients were obtained. We genotyped the patient and his family (pedigree: 9,14,32-proband-,42) for MTHFR 677 and 1298. For genetic analysis, 5 ml of blood was drawn into tubes containing EDTA from each patient. DNA were extracted using a commercial kit (QIAamp DNA mini kit; Qiagen, Hilden, Germany). Genotyping of MTHFR alleles was performed in all subjects by real-time polymerase chain reaction (RT-PCR) using allelic discrimination. The three genotypes were defined as follows: CC, normal homozygous (wild type); CT, heterozygous; and TT mutant homozygous for C677T and AA, normal homozygous (wild type); AC, heterozygous; and CC mutant homozygous for A1298C.

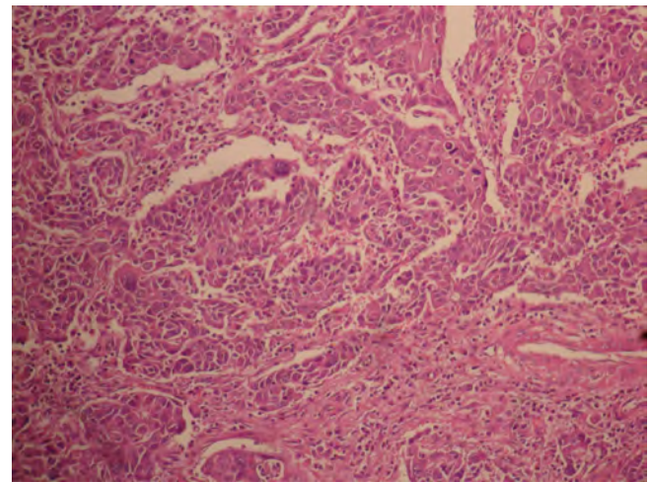

Figure 1. High grade invasive urothelial cancer consists of epithelial islet cells with large hyperchromatin nucleolus which have pleomorphism.

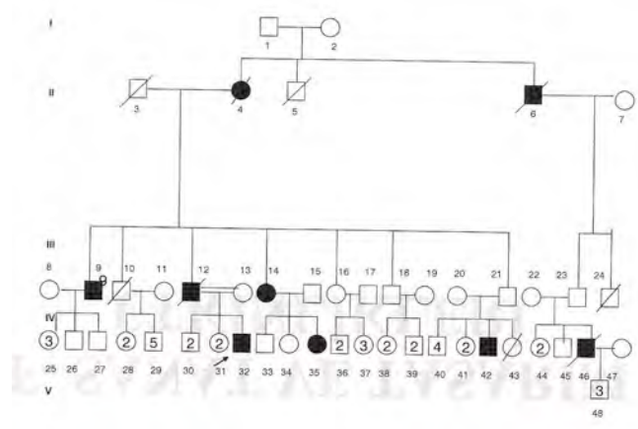

Figure 2. The pedigree of the family.

Discussion

There is a strong evidence about the interaction between gene variations involved in folate metabolism and risk of bladder cancer. These variations act additively to increase the risk for bladder cancer and this risk is increased among smokers carrying altered genotypes. Many studies focusing on MTHFR variants relationship with the risk of bladder cancer have produced conflicting results. These conflicting results may be explained by the metabolic role of the MTHFR enzyme, which is involved

in both DNA methylation and DNA synthesis. The increased risk for the variant MTHFR activity could influence the availability of methyl donors by altering S-adenosyl-methionine levels, and potentially, the methylation status of key tumor suppressor or promoter genes involved in bladder carcinogenesis [3]. Here we report a family with bladder cancer. MTHFR 677*T and 1298*C variants in the patients in this family had been performed. The MTHFR 1298 CT genotype was heterozygote in all of the patients in this family who were also diagnosed as transitional bladder cancer. MTHFR 677*T and 1298*C variants were both heterozygote in the proband.

In previous studies, for the association between the MTHFR C677T and A1298C polymorphisms and bladder cancer risk, it has been observed that the variant genotype MTHFR 677TT was associated with an increased risk of bladder cancer, compared with the wild-type homozygote 677CC. Folate deficiency leads to decreased DNA methylation and such insufficiency may result in carcinogenesis by inducing genomic instability or activation of oncogenes [2]. In a meta-analysis, 13 different articles were identified to evaluate the association between C677T or A1298C polymorphisms in the MTHFR gene and the risk for bladder cancer. According to this meta-analysis, there was no significant association between the C677T polymorphism and the susceptibility to bladder cancer risk in the overall analysis, but significant relationships were detected in the mixed and Asian populations rather than in Europeans and Africans. This is important, because the allele and genotype distribution of MTHFR C677T locus is different in different races [4]. Safarinejad et al [5] found that the 1298C allele (CA+CC, heterozygotes and homozygotes) was significantly associated with increased risk of bladder cancer in Asians. Similarly, individuals who carried the 1298 CC genotype (homozygote) had a higher risk for bladder cancer in Asians. Moreover, this increased association was also found in Africans. However, the CC genotype (homozygosity) played a protective role for bladder cancer in Europeans [5]. In a study, association between MTHFR C677T and gastric cancer, leucemia and colorectal cancer were also among the most noteworthy associations. Because of its role in a key pathway, the MTHFR C677T variant may have a true impact on cancer risk [6]. In a study by Ozarda et al [13], frequencies of C and T alleles and also frequencies of TT and CC genotypes were investigated in 402 healthy individuals. The frequency of MTHFR T677T genotype was found as 7.7% and the frequency of MTHFR C677T genotype was found as 40%, in males. In females, these rates were as 9.1% and 42.2%, respectively [7].

MTHFR genes play a central role in folate metabolism, and studies have revealed that the cancer risk associated with MTHFR polymorphisms may be modulated by folate intake. The decreased expression of MTHFR by hypermethylation due to the C677 polymorphism may cause an increased risk of DNA hypomethylation of oncogenes, which may not be corrected by other DNA repair enzymes, resulting in a higher susceptibility to bladder cancer in carriers of the 677TT genotype [8].

In conclusion, according to the literature, the MTHFR C677T and A1298C polymorphisms have an effect on increasing risk of bladder cancer [7]. In this report, a family with transitional bladder cancer have also MTHFR A1298C heterozygosity which supports the association between MTHFR variants and bladder cancer. This finding should be further validated by prospective and larger studies with more diverse ethnic groups and more detailed environmental exposure data.

Competing interests

The authors declare that they have no competing interests.

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