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RAPID COMMUNICATION

DNMT3B 579 G>T promoter polymorphism and risk of esophagus carcinoma in Chinese

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Abstract

AIM: To investigate the relationship between 579 G>T polymorphisms in the DNMT3B gene, which is involved in de novo methylation and associated with the risk of esophagus cancer (EC) in Chinese.

METHODS: DNMT3B 579 G>T genotypes were determined by PCR-RFLP in 194 EC patients and 210 healthy controls matched for age and sex, who did not receive radiotherapy or chemotherapy for newly diagnosed and histopathologically confirmed EC.

RESULTS: In control subjects, the frequency of T/T and G/T genotypes, and T and G alleles was 80.5%, 19.0%, 90.0% and 10.0%, respectively. The distribution of genotypes and allelotypes in the EC patients was not significantly different from that in the controls. When stratified by sex and age, there was still no significant association between the risks of EC and GT and GG genotypes. This study also showed a distinct difference in the distribution of DNMT3B and single nucleotide polymorphism (SNP) between Chinese and Koreans.

CONCLUSION: DNMT3B 579 G>T polymorphism may not be a stratification marker to predict the susceptibility to EC, at least in Chinese. DNMT3B promoter SNP is diverse in ethnic populations.

Key words: Esophagus cancer; DNMT3B; Methylation; Polymorphism

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INTRODUCTION

Esophagus carcinoma (EC) is one of the most common malignancies and the main cause of cancer-related death in the world. Because symptoms typically remain absent until late in the course of disease, most cancers are detected at an advanced stage when prognosis is poor. Therefore, it is important to investigate the genetic and epigenetic variation in susceptibility to esophagus carcinogenesis and identify the markers that will facilitate identification of individuals at risk of esophagus carcinogenesis.

DNA methylation is a major epigenetic modification involving the addition of a methyl group to the 5' position of a cytosine in a CpG dinucleotide. A number of studies suggested that aberrant DNA cytosine methylation may play an important role in carcinogenesis[1-5]. DNMT3A and DNMT3B are required for the establishment and maintenance of genomic methylation patterns and proper murine development[6-9]. Both genes are up-regulated to different degrees in some malignancies, including colon cancer and EC[10-14]. Recently, several candidate single nucleotide polymorphisms (SNPs) in the DNMT3B gene have been deposited in public databases. Although the functional effects of these polymorphisms have not been elucidated, some studies showed that some of these variants may influence the DNMT3B activity on DNA methylation,

thereby modulating the susceptibility to lung cancer, breast cancer and gastric cardiac adenocarcinoma[15-17]. The DNMT3B gene contains a single G>T SNP in the transcription start site of the promoter region (-579 bp from exon 1B), and this probably affects gene function[18]. Some studies suggested that DNMT3B -579 G>T may modify susceptibility to tumors. Although conflicting results have been reported in different tumor types, the heterozygous genotypes have a significantly reduced risk of developing lung and colon cancer[19-21]. However, no report on the association between this allele and the development of EC is available. This study was to investigate the association between this polymorphism and EC in Chinese.

MATERIALS AND METHODS

Study population

This case-control study included 194 EC patients and 210 healthy controls. EC was histopathologically confirmed in the 194 patients during surgery at the Zhongda Hospital of Southeast University and Tumor Hospital, Nanjing, China. The control subjects were selected from cancer-free subjects who visited the same hospital for a regular physical examination and volunteered to participate in the epidemiology survey during the same period. We defined a healthy subject as a person free of disease (including no history of cancer) at health check-up. The controls were matched for age and sex with the patients (Table 1). All patients and controls were ethnically Chinese and resided in Jiangsu Province or in its surrounding regions.

DNA extraction

Five milliliters of venous blood was drawn from each subject into vacuum tubes containing EDTA and stored at 4℃. Genomic DNA was extracted within one week after sampling by proteinase K digestion and salted out as previously described[19].

DNMT 3B genotyping

Transition from G to T of the DNMT3B SNP creates a *PvuII* restriction site, which can be exploited for genotyping by PCR and subsequent restriction fragment length polymorphism (RFLP) analysis. PCR was performed in a volume of 25 μL containing 100 ng of DNA template, 10 × PCR master mix (Promega, USA), and 10 pmol/L each of sense primer (5'-GAGGTCTCATTATGCCTAGG-3') and antisense primer (5'-GGGAGCTCACCTTCTAGAAA -3'). For PCR amplification, an initial denaturation at 94℃ for 5 min was followed by 30 cycles at 94℃ for 30 s, at 57℃ for 30 s, at 72℃ for 30 s, and a final extension at 72℃ for 7 min. The PCR products were digested overnight with 5 units of *PvuII* (New England Biolabs, Beverly, Mass.) at 37℃ and separated on 2% agarose gels. RFLP bands were visualized under UV light with ethidium bromide staining. The DNMT3B T/T genotype was expected to show two DNA bands at the positions of 132 bp and 93 bp, whereas the G/G genotype was expected to show a single band (225 bp), and the heterozygote was expected to have three bands (225 bp, 132 bp, 93 bp). For quality control, genotyping analysis was performed blindly with respect to case/control status and repeated twice for all subjects.

Table 1 Distribution of selected variables in esophagus cancer patients and control subjects *n* (%)

Variables	Patients (*n* = 194)	Control (*n* = 210)	*P*
Age (yr)			> 0.05
< 40	1 (0.5)	2 (0.9)	
40-60	117 (60.3)	110 (52.4)	
61-80	76 (39.2)	98 (46.7)	
Sex			> 0.05
Male	150 (77.3)	146 (69.5)	
Female	44 (22.7)	64 (30.5)	

DNA sequencing analysis

To confirm the genotyping results, selected PCR-amplified DNA samples were examined by DNA sequencing. The PCR fragments were recovered from agarose gel followed by purification with a DNA clean-up kit (Wizard SV Gel and PCR Clean-up System, Promega). DNA sequences of the PCR products were determined using the PCR sense primer with an Applied Biosystems model 377 sequencer (PE Applied Biosystems, Warrington, UK). The results of genotyping were 100% concordant.

Statistical analysis

Patients and controls were compared using Student's *t*-test for continuous variables and chi square (χ^2) test for categorical variables. Hardy-Weinberg equilibrium was tested with a goodness-of-fit χ^2 test with one degree of freedom to compare the observed genotype frequencies with the expected genotype frequencies among the subjects. Comparison of the DNMT3B genotype and allelotype distribution in the study groups was performed by means of two-sided contingency tables using χ^2 test or Fischer's exact test. The odds ratio (OR) and 95% confidence interval (CI) were calculated using an unconditional logistic regression model and adjusted for age and gender accordingly. $P < 0.05$ was considered statistically significant.

RESULTS

The demographics of the cases and controls enrolled in this study are shown in Table 1. There were no significant differences in the mean age and sex distribution between cases and controls, suggesting that the matching based on these two variables was adequate. There was no evidence of a deviation from Hardy-Weinberg equilibrium among the cases or controls. The mean age of the patients and controls was 59.6 years (± 10.2 years; range, 34-80 years) and 59.6 years (± 10.2 years; range, 34-80 years), respectively.

All the patients and controls were successfully genotyped for the DNMT3B polymorphism (Figure 1). The genotyping by PCR-RFLP analysis was completely confirmed by DNA sequencing analysis, and the results of PCR-RFLP genotyping and sequencing analysis were also 100% concordant (Figure 2). The distribution of DNMT3B 579 G>T polymorphism was in Hardy-Weinberg equilibrium. The frequency of G allele in control subjects (0.10) was different from that in the previous

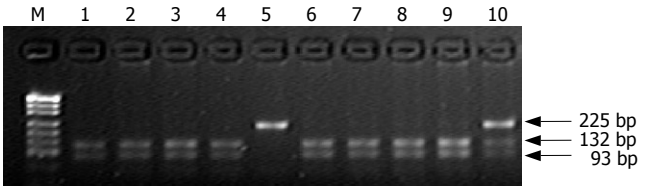

Figure 1 PCR-based restriction fragment length polymorphism genotyping of DNMT3B 579 G>T. Lanes 1-4, 6-9: TT variants; lane 5: GG wild type; lane 10: GT heterozygote.

Table 2 DNMT3B genotype and allele frequency in Chinese and Koreans

	TT	GT	GG	G allele frequency (%)
Chinese	169 (80.5)	40 (19.0)	1 (0.5)	10.0
Korean	153 (61.7)	91 (36.7)	4 (1.6)	20[b]

[b]$P < 0.01$ *vs* Chinese.

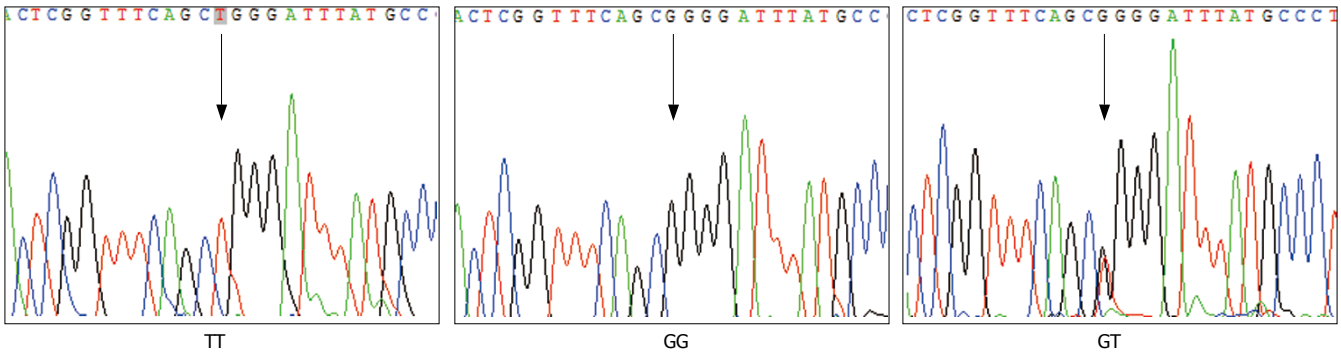

Figure 2 Sequencing results for each of the PCR products from different genotypes. The SNP sites are indicated by the arrowhead. The results were completely matched to the corresponding results derived from PCR-RFLP genotyping.

study among Koreans (0.20)[21]. The distributions of DNMT3B 579 G>T genotypes in Chinese and Koreans are shown in Table 2.

The distributions of DNMT3B 579 G>T genotypes in controls and patients are shown in Table 3. The genotype distributions of both polymorphisms in the controls were in Hardy-Weinberg equilibrium. No significant deviation was observed in the genotype distributions of both polymorphisms between overall esophagus cancer patients and controls. Then we stratified the results by sex and age, patients and controls were found to be slightly different with respect to the genotype distribution (Table 4). Combined GG and GT genotypes were found to have a little higher OR in male esophagus cancer patients and the group under the age of 59 years (males: OR 1.35 ; 95% CI, 0.76-2.39; under 59: OR 1.47 ; 95% CI, 0.74-2.90). However, combined GG and GT genotypes showed no significant association between DNMT3B 579 G>T polymorphism and the risk of esophagus cancer.

Table 3 DNMT3B genotype and allele frequency in patients and control subjects and their association with esophagus cancer *n* (%)

	Case patients (n = 194)	Control subjects (n = 210)	OR (95% CI)
DNMT3B 579 G>T			
TT	151 (77.8)	169 (80.5)	
GT	43 (22.2)	40 (19.0)	1.17 (0.73-1.90)
GG	0 (0)	1 (0.50)	
G allele (%)	11.1	10.0	

Table 4 Stratification analysis of DNMT3B 579 G>T genotype frequencies in esophagus cancer patients and controls, adjusted OR (95% CI)

Variable	TT genotype Case/control	GT + GG genotype Case/control	Odds ratios of GT + GG genotype
Age			
< 60	81/89	24/18	1.47 (0.74-2.90)
⩾60	70/80	19/23	0.94 (0.48-1.88)
Sex			
Male	116/120	34/26	1.35 (0.76-2.39)
Female	35/49	9/15	0.84 (0.33-2.14)

DISCUSSION

Single nucleotide polymorphism (SNP) is the most common form of human genetic variation, and may contribute to an individual's susceptibility to cancer. Studies suggested that some variants in the promoter region of genes may affect either the expression or activity levels of enzymes[1,18,22] and therefore may be mechanistically associated with cancer risk. It has been recently shown that SNP of the DNMT3B promoter 579 G>T (from exon 1B transcription start site) decreases the susceptibility of an individual to lung and colon cancer[20,21], suggesting that DNMT3B promoter 579 G>T polymorphism can be used as a risk factor for cancer to evaluate the population susceptible to tumors. However, it was also reported that there is no association between polymorphism of 579 G>T and head and neck squamous cell carcinoma[23]. However, to the best of our knowledge, the relative significance of SNP in the genetic susceptibility to esophagus cancer has not yet been disclosed. In the

current study, we investigated the influence of DNMT3B polymorphisms on the risk of esophagus cancer in a hospital-based case-control study.

This is the first study of DNMT3B polymorphism in esophagus cancer. We investigated the influence of 579 G>T polymorphism in the DNMT3B gene on the risk of esophagus cancer. Individuals carrying G allele in the DNMT3B gene were found to have a nearly consistent risk of EC compared with those carrying T allele. Then we stratified the results by sex and age, patients and controls. Combined GG and GT genotypes showed no significant association between DNMT3B 579 G>T polymorphism and risk of esophagus cancer, suggesting that 579 G>T polymorphism in the DNMT3B gene cannot be used as a marker of genetic susceptibility to esophagus cancer even in young individuals. Our study showed that DNMT3B polymorphism was not associated with the risk of esophagus carcinoma, at least in the study population, although other studies reported a decreased risk of lung and colon cancer in those harboring G allele. Since the different variants of DNMT3B may alter catalytic activity and are expressed in a tissue specific manner[24-27] and the repression of DNMT3B activity does not result in re-expression of all hypermethylated tumor suppressor genes in some cell systems[28-31], it is therefore important to explore the complex interplay of DNMTs in different tumor types.

In this study, a distinct difference was found in the distribution of DNMT3B SNP between Chinese and Koreans. However, few G/G genotypes were found in both populations. Additionally, the frequency of G/T genotype in Chinese was lower than that in Koreans. The great diversity in DNMT3B SNP distribution in different ethnic populations remains unknown.

In conclusion, the DNMT3B gene may not be involved in the development of esophagus cancer. Further studies with a larger sample are required to confirm our findings, to understand the role of DNMT3B polymorphisms in determining the risk of esophagus cancer, and to clarify the association of DNMT3B polymorphism with esophagus cancer in different ethnic populations.

COMMENTS

Background

DNA methylation is a major epigenetic modification involving the addition of a methyl group to the 5' position of a cytosine in CpG dinucleotide. DNMT3A and DNMT3B are required for the establishment and maintenance of genomic methylation patterns. Single nucleotide polymorphisms (SNPs) in the DNMT3B gene may influence DNMT3B activity on DNA methylation, thereby modulating the susceptibility to some cancer.

Research frontiers

Some variants in the promoter region of genes may affect either the expression or activity levels of enzymes and therefore may be mechanistically associated with cancer risk. It has been recently reported that SNP of the DNMT3B promoter 579 G>T (from exon 1B transcription start site) decreases the susceptibility of an individual to lung and colon cancer. However, it was also reported that there is no association between polymorphism of 579 G>T and head and neck squamous cell carcinoma. The relative significance of SNP in genetic susceptibility of an individual to cancer is diverse in different populations.

Innovations and breakthroughs

It is important to investigate the genetic and epigenetic variation in susceptibility to esophagus carcinogenesis and identify markers that will facilitate identification of individuals at risk of esophagus carcinogenesis. Although no significant association was found between DNMT3B 579 G>T polymorphism and risk of esophagus cancer, this is the first study of DNMT3B polymorphism in esophagus cancer. This study also showed the significance of great diversity in DNMT3B SNP distribution in different ethnic populations and their susceptibility to cancer.

Applications

A distinct difference was found in the distribution of DNMT3B SNP between Chinese and Koreans in this study. The significance of great diversity in DNMT3B SNP distribution in different ethnic populations remains unknown. These results suggest that the DNMT3B gene may not be involved in the development of esophagus cancer. Future studies of other DNMT3B sequence variants and their biologic function are needed to understand the role of DNMT3B polymorphisms in determining the risk of esophagus cancer.

Peer review

The association between DNMT3B 579 G>T polymorphism and the risk of esophagus cancer in Chinese was studied. The results show that the DNMT3B 579 G>T polymorphism was not associated with the risk of esophagus carcinoma, at least in the study population. This study also showed the significance of great diversity in DNMT3B SNP distribution in different ethnic populations and their susceptibility to cancer.

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