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Association between CYP1B1 Gene Polymorphisms and Risk Factors and Susceptibility to Laryngeal Cancer

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The aim of this study was to investigate the association between polymorphism of the cytochrome P450 1B1 (CYP1B1) gene, a metabolic enzyme gene, and the susceptibility to laryngeal cancer among the Chinese Han population.

Material/Methods: In a case-control study, we investigated polymorphisms in the CYP1B1 gene (rs10012, rs1056827, and rs1056836) with a real-time quantitative polymerase chain reaction (PCR) assay (TaqMan). The study was conducted with 300 Chinese Han patients with laryngeal cancer and 300 healthy Chinese Han subjects in a control group. We also studied the interactions between genetic polymorphism and risk factors such as smoking and alcohol consumption in the pathogenesis of laryngeal cancer.

Results: There were statistically significant differences in the distributions of the rs1056827 and rs1056836 genotypes between the 2 groups. Regarding rs1056827, carriers of the T allele had a significantly higher risk of laryngeal cancer than the G-allele carriers (OR=1.4339, 95% CI: 1.1268–1.8247; P=0.0034). The difference was still statistically significant after adjusting for factors such as age, sex, smoking, and drinking (adjusted OR=1.743, 95% CI: 1.124–3.743, P<0.001). However, regarding rs1056836, the G allele carriers had a significantly lower risk of laryngeal cancer than the C allele carriers (OR=0.5557, 95% CI: 0.3787–0.8154; P=0.0027). The difference was statistically significant even after adjusting for factors such as age, sex, smoking, and drinking (adjusted OR=0.5641, 95% CI: 0.3212–0.8121, P=0.001). Subjects who carry the C-T-C haplotype have a significantly increased incidence of laryngeal cancer. We also found that CYP1B1 rs1056827 polymorphism had synergistic effects with smoking or alcohol consumption regarding the risk of laryngeal cancer.

Conclusions: CYP1B1 gene polymorphism is closely related to the onset of laryngeal cancer. There is a mutually synergistic effect between smoking, alcohol consumption, and CYP1B1 gene polymorphisms regarding laryngeal cancer.

MeSH Keywords: **Laryngeal Neoplasms • Polymorphism, Single Nucleotide • Steroid 11-beta-Hydroxylase**

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2627 4 — 23

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Background

Laryngeal cancer is a common type of malignant tumor in the head and neck, and the incidence of this type of tumor is increasing yearly [1]. The etiology of laryngeal cancer is not clear. It is believed that this cancer is the result of the combined effects of multiple factors, primarily environmental and genetic factors [2,3]. Studying the genetic factors associated with laryngeal cancer from the perspective of molecular genetics and screening possible susceptibility genes via relevance analysis are of great importance in discovering the pathogenesis of laryngeal cancer. The metabolism of pro-carcinogens, such as polycyclic aromatic hydrocarbons and heterocyclic amines, can be catalyzed by cytochrome P450 1B1 (CYP1B1) [4–6], resulting in carcinogen activation and the formation of cytotoxic substances and DNA intermediates [7,8]. This action of CYP1B1 may be the mechanism responsible for the susceptibility to tumors. To date, more than 50 polymorphic *loci* have been identified that affect the coding of the CYP1B1 protein. Of these *loci*, rs10012, rs1056827 and rs1056836 affect the metabolic activity of this enzyme toward carcinogens by changes in the corresponding amino acids [9–11]. Trubicka et al. [12] genotyped 597 cancer patients and 597controls for these 3 CYP1B1 SNPs, which have previously been shown to be associated with altered enzymatic activity [9–11]. The authors utilized the 3 SNPs to construct 8 different haplotypes. Haplotypes of rs1056827 and rs10012 or rs1056827 and rs1056836 revealed an association with colorectal cancer. Xu et al. [13] performed a meta-analysis to clarify the association of these 3 SNPs with lung cancer and found the CYP1B1 rs10012, rs1056827 and rs1056836 genotypes are low-penetrance risk factors for developing lung cancer. However, the relation between these 3 SNPs and laryngeal cancer remains unclear.

This study analyzed the relationship between the genetic variations in these 3 *loci* and susceptibility to laryngeal cancer through a case-control study, which provided important clues for the prevention and early diagnosis of laryngeal cancer.

Material and Methods

Subject selection

Three hundred patients who had been diagnosed with laryngeal cancer in Kunshan Chinese Medicine Hospital, Jiangsu Province and the Department of Otolaryngology, Head and Neck Surgery, Nanjing General Hospital of the Nanjing Military Region from August 2001 through February 2014 were selected for the case group in the study. The inclusion criteria were as follows: 1) the subject's primary tumor was diagnosed as laryngeal squamous cell cancer by way of a histopathological examination; 2) the subject had not been treated with chemotherapy prior to acquiring blood samples; 3) the subject's blood specimens were well preserved; 4) the subject had complete clinical data; and 5) the subject was of Han ethnicity, and there was no kinship with the other subjects. The 300 subjects in the control group were healthy people who had undergone a physical examination during the same period at the physical exam centers of the same hospitals. In addition to the criteria numbered 2)-5) mentioned above, the inclusion criteria for the control group included the following: 1) the subject had no history of tumor, and no tumor was found during the physical exam; 2) the subject had no genetic family history of tumors; and 3) the subject had no history of occupational exposure to carcinogenic substances such as radiation, toxic gases, etc. No significant differences in gender or age were identified between the control and case groups according to frequency pairing. This study was approved by the academic ethics committee of Jiangsu Province Academy of Traditional Chinese Medicine. An informed consent form was signed by each subject.

Genomic DNA extraction

For all of the subjects, 4-ml samples of venous blood were placed in tubes with ethylenediaminetetraacetic acid (EDTA) anticoagulant for cryopreservation at –70°C. The DNA extraction was performed using the AxyPrep whole blood genomic DNA kit (Axygen Biosciences, CA, USA) according to the manufacturer's instructions.

Genotyping

The genotyping was performed with the 7900HT Fast Real-Time PCR System and TaqMan genotyping kits manufactured by Applied Biosystems (CA, USD),as described previously [14]. Briefly, The TaqMan SNP Genotyping Assays were performed using the method of Taq amplification. In the 5' nuclease assay, discrimination occurs during the polymerase chain reaction (PCR) because of allele-specific fluorogenic probes that, when hybridized to the template, are cleaved by the 5' nuclease activity of Taq polymerase. The probes contain a 3' minor groove-binding group (MGB) that hybridizes to single-stranded targets with greater sequence specificity than ordinary DNA probes. This reduces nonspecific probe hybridization and results in low background fluorescence in the 5' nuclease PCR assay (TaqMan, ABI). Cleavage results in increased emission of a reporter dye. Each 5' nuclease assay requires 2 unlabeled PCR primers and 2 allele-specific probes. Each probe is labeled with 2 reporter dyes at the 5' end. In the present study, VIC® and FAM™ were used as the reporter dyes. The primers and probes used in the TaqMan SNP Genotyping Assays (ABI) were chosen based on information available at the ABI website (*http://myscience.appliedbiosystems.com*). Polymerase chain reaction amplification was performed using 6 mL of TaqMan Universal Master Mix,

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No AmpErase UNG (2×; ABI) in a 12-mL final reaction volume containing 2 ng of DNA, 0.22 uL of TaqMan SNP Genotyping Assay Mix (20× or 40×) primers at a concentration of 900 nmol/L each, and probes at a final concentration of 200 nmol/L each.

Thermal cycling conditions were as follows: 50°C for 2 minutes, 95°C for 10 minutes, 40 cycles of 95°C for 15 seconds, and 62°C for 1 minute. Thermal cycling was performed using the GeneAmp 9700 system. Each 96-well plate contained 80 DNA samples of an unknown genotype and 4 reaction mixtures containing reagents but no DNA (control). The control samples without DNA are a necessary part of the Sequence Detection System (SDS) 7700 signal processing, as outlined in the TaqMan Allelic Discrimination Guide (ABI). The plates were read on the

SDS 7700 instrument with the end-point analysis mode of the SDS version 1.6.3 software package (ABI). The genotypes were determined visually based on the dye-component fluorescent emission data depicted in the x-y scatterplot of the SDS software. The genotypes were also determined automatically by the signal processing algorithms of the software. The results of each scoring method were saved in 2 separate output files for later comparison.

Assessment of smoking and alcohol consumption

Cigarette smoking was assessed using a smoking index (SI) defined as follows: SI=number of cigarettes per day/20× number of years of smoking. A light smoker is a subject with an SI equal to or below 20, while a heavy smoker is a subject with an SI greater than 20 [15]. A drinking index (DI) was used to assess alcohol consumption and was calculated as follows: DI=daily alcohol consumption (ml)× number of years of drinking. Subjects were categorized as light drinkers (DI≤60) or heavy drinkers (DI>60) [16].

Statistical analysis

The SPSS 17.0 statistical software was used for statistical analyses. The Hardy-Weinberg equilibrium test was used to test the group representation of the CYP1B1 genotype and determine the allele frequency distribution in the case and control groups. SHEsis software was used for the haplotype analysis, including haploid construction and linkage disequilibrium. A 4-fold table test was used to assess the differences between the genotype and allele frequencies. An unconditional logistic regression model was used to calculate the odds ratio (OR) values and 95% confidence intervals (95% CIs) for each genotype and the risk of laryngeal cancer. A P value <0.05 was considered statistically significant. To assess the association of each SNP with laryngeal cancer, we used a Bonferroni correction to control for the number of variants tested; this was 3, so the probability value, 0.017, was considered to be significant.

Table 1. The characteristics of the participants.

Variables	Case group (n=300), mean (SD)	Control group (n=300), mean (SD)	P values
Age (years)	64.2 (10.3)	64.8 (10.6)	0.232
Sex			0.886
Male	271	273	
Female	29	27	
Smoking			<0.001
No-smoking	43	105	
Current smoking (SI)	257	195	
≤20	40	101	
>20	217	94	
Drinking			<0.001
No-drinking	101	155	
Current drinking (DI)	199	145	
≤60	51	83	
>60	148	62	

Results

General information

Table 1 has the distribution of risk factors for the case and control groups. There were significantly higher proportions of subjects who smoked and consumed alcohol in the case group than in the control group (Both P<0.05).

Distributions of alleles and genotypes

Table 2 displays the genotype and allele frequencies of the 3 polymorphic *loci*. All the samples were consistent with Hardy-Weinberg equilibrium (P>0.05), and the selected sample was representative of the group. Statistically significant differences were found between the case and control groups when comparing the distributions of polymorphisms for rs1056827 and rs1056836. Regarding rs1056827, carriers of the T allele had a significantly higher risk of laryngeal cancer than the G-allele carriers (OR=1.4339, 95% CI: 1.1268–1.8247; P=0.0034). The difference was still statistically significant after adjusting for factors such as age, gender, smoking and drinking (adjusted OR=1.743, 95% CI: 1.124–3.743, P<0.001). However, regarding

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Table 2. Distribution of genotype and alleles of CYP1B1 gene.

SNPs	Case group(n=300)	Control group (n=300)	OR (95% CI)	P value
rs10012				
Genotype				
CC	208	197	1.00	
CG	83	88	0.8933 (0.6247–1.2774)	0.5363
GG	9	15	0.5683 (0.2431–1.3283)	0.192
Allele				
C	499	482	1.00	
G	101	118	0.8268 (0.6164–1.1090)	0.2043
rs1056827				
Genotype				
GG	83	129	1	
GT	209	165	1.9687 (1.3969–2.7745)	0.0001
TT	8	6	2.0723 (0.6941–6.1873)	0.1917
Allele				
G	375	423	1.00	
T	225	177	1.4339 (1.1268–1.8247)	0.0034
rs1056836				
Genotype				
CC	258	227	1.00	
CG	38	68	0.4917 (0.3182–0.7598)	0.0014
GG	4	5	0.7039 (0.1868–2.6530)	0.604
Allele				
C	554	522	1.00	
G	46	78	0.5557 (0.3787–0.8154)	0.0027

rs1056836, the G allele carriers had a significantly lower risk of laryngeal cancer than the C allele carriers (OR=0.5557, 95% CI: 0.3787–0.8154; P=0.0027). The difference was statistically significant even after adjusting for factors such as age, gender, smoking and drinking (adjusted OR=0.5641, 95% CI: 0.3212–0.8121, P=0.001). A comparison of the polymorphism distribution for rs10012 between the case and control groups showed no significant difference (P=0.2043), and there was no significant correlation with the risk of laryngeal cancer.

Haplotype analysis

As shown in Table 3, 7 haplotypes were constructed from the 8 possible haplotype configurations, and only 2 of these haplotypes were associated with the risk of laryngeal cancer. The most common haplotype was C-G-C (constructed by rs10012, rs1056827, and rs1056836), which accounted for 60.3% and 65.0% of the subjects in the case and control groups, respectively, indicating that C-G-C was a low risk factors for laryngeal cancer (P=0.002). Compared to carriers of the C-G-C haplotype, C-T-C haplotype carriers had a significantly higher risk of laryngeal cancer (OR=3.017, 95% CI: 1.869–4.868, P<0.001).

The synergistic effect of rs1056827, smoking and drinking on laryngeal cancer

Table 4 describes the influence of the combined effects of the 3 polymorphic *loci* with smoking and drinking on the risk of laryngeal cancer. In the non-smoking group, the OR for the risk of laryngeal cancer was 1.7902 (95% CI: 0.8123–3.9453) for carriers of CYP1B1 rs1056827 GT + TT, while in the smoking group, the corresponding OR was 6.3465 (95%CI: 3.1243–12.8920), which was significantly different (P<0.001); Furthermore, in carriers of T allele with SI>20, the OR was 12.648 (95%CI: 6.0136–26.6026), which indicated that there was a significant

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Table 3. Distribution of haplotype in case and control groups.

Haplotype	Case groups (allele number)		Control group (allele number)		OR (95%CI)	P value
C-G-C	362	(60.0%)	390	(65.0%)	1 (ref.)	0.002
G-G-C	5	(0.8%)	2	(0.3%)	2.6934 (0.5193–13.9690)	0.2381
C-T-C	70	(11.7%)	25	(4.1%)	3.0166 (1.8693–4.8679)	<0.0001
G-T-C	112	(18.7%)	121	(20.2%)	0.9972 (0.7431–1.3382)	0.9852
C-G-G	22	(3.3%)	32	(5.3%)	0.7407 (0.4225–1.2984)	0.2946
C-T-G	12	(2.0%)	8	(1.3%)	1.6160 (0.6531–3.9985)	0.2991
G-T-G	17	(2.8%)	24	(4.0%)	0.7631 (0.4034–1.4437)	0.4059

Table 4. Interaction between smoking, drinking, and rs1056827.

	GG				GT+TT			
	Case group	Control group	OR (95% CI)	P value	Case group	Control group	OR (95% CI)	P value
Smoking								
No-smoking	11	40	1 (ref.)		32	65	1.7902 (0.8123–3.9453)	0.1486
Smoking (SI)	72	89	2.9418 (1.4091–6.1415)	0.0041	185	106	6.3465 (3.1243–12.8920)	0.0001
SI≤20	15	41	1.3304 (0.5454–3.2450)	0.5303	25	60	1.5152 (0.6712–3.4203)	0.3172
SI>20	57	48	4.3182 (1.9997–9.3250)	0.0002	160	46	12.6482 (6.0136–26.6026)	0.0001
Drinking								
No-drinking	23	62	1 (ref.)		78	93	2.2609 (1.2846–3.9790)	0.0047
Drinking (DI)	60	67	2.4140 (1.3356–4.3631)	0.0035	139	78	4.8038 (2.7631–8.3516)	0.0000
DI≤60	8	36	0.5990 (0.2428–1.4782)	0.1320	43	47	2.4662 (1.3102–4.6422)	0.0052
DI>60	52	31	4.5217(2.3528–8.6900)	0.0000	96	31	8.3478 (4.4601–15.6243)	0.0000

interaction between smoking and rs1056827 polymorphism for the risk of the laryngeal cancer. In the non-drinking group, the OR for the risk of laryngeal cancer was 2.2609 (95% CI: 1.2846–3.9790) for carriers of CYP1B1 rs1056827 GT + TT; however, in the drinking group, the corresponding OR was 4.8038 (95%CI: 2.7631–8.3516 P<0.001), which was significantly higher than the OR value obtained by multiplying the risks of laryngeal cancer associated with alcohol consumption and genetic polymorphism obtained in the univariate analyses. These data indicated that CYP1B1 rs1056827 polymorphism had any synergistic effects with smoking or alcohol consumption regarding the risk of laryngeal cancer. However, neither of the other 2 *loci* had synergistic effects with smoking and drinking (data not shown).

Discussion

This case-control study of the Han Chinese population demonstrates that the CYP1B1 gene polymorphisms rs1056827 and rs1056836 are closely related to the risk of laryngeal cancer. The mutant T allele of the CYP1B1 rs1056827 polymorphism is positively correlated with the risk of laryngeal cancer, while the mutant G allele of CYP1B1 rs1056836 has a protective effect by reducing the risk of laryngeal cancer.

The CYP1B1 rs1056827 polymorphism locus is located in the second exon of chromosome 2p21.22. A mutation of this allele can cause a corresponding change in the amino acid from Ala to Ser. Singh et al. [17] reported a CYP1B1 rs1056827 mutation

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that was associated with head and neck cancer, and the mutant genotype increased the risk of head and neck tumors. Jawarowska et al. [18] also found a CYP1B1 rs1056827 mutant allele that can increase the risk of laryngeal cancer. This study also found that carriers of the CYP1B1 rs1056827 mutant allele had a significantly higher risk of laryngeal cancer compared with carriers of the wild type gene. All of the above indicate that CYP1B1 rs1056827 is a gene associated with the risk of laryngeal cancer, and a mutant genotype of CYP1B1 rs1056827 can increase the risk of laryngeal cancer. However, the mechanism of action involved in CYP1B1 gene polymorphism regarding laryngeal cancer is not yet clear.

The CYP1B1 gene rs1056836 polymorphism locus is located in the third exon of chromosome 2p21-22. A mutation of this allele can cause a corresponding change in the amino acid from Leu to Val. Church et al. [19] found that smokers who carried the mutant allele had a significantly higher risk of lung cancer. However, the relationship between genetic polymorphisms at this locus and lung cancer susceptibility is not clear. Tai et al. [15] reported that CYP1B1 gene rs1056836 polymorphism was irrelevant to the susceptibility to hypopharyngeal cancer and laryngeal cancer. However, Trubicka et al. [12] reported that expression levels of the mutant G genotype in colorectal cancer patients were significantly lower than those in the control group, which indicated that the presence of the mutant allele may have a protective function by reducing the risk of colorectal cancer in susceptible populations. This finding is consistent with the results of our study: the expression of the CYP1B1 rs1056836 heterozygous genotype was significantly reduced in the patient group, suggesting that the C>G allele mutation has a protective effect by reducing the risk of laryngeal cancer. Possible reasons contributing to these different results include the difference in the genetic constitution of different races, other confounding factors such as the effects of other polymorphic *loci*, the sample size and the statistical analyses. However, we did not find any correlation of CYP1B1 rs10012 polymorphisms with laryngeal cancer, although the mutation leads to a change of the amino acid from Arg to Gly.

Our haplotype analysis indicated that C-G-C is the most common haplotype configuration. The C-T-C haplotype confers a significantly higher risk of laryngeal cancer than the other haplotypes. This result suggests that the risk of laryngeal cancer will increase with an increased number of risk *loci*, and the risk will decrease with an increased number of protective *loci*.

Epidemiological data indicate that environmental factors, especially tobacco and alcohol use, are important causes of laryngeal cancer [20,21]. The CYP1B1 metabolic enzymes can metabolize the pro-carcinogens in tobacco (such as aromatic ring hydrocarbons, heterocyclic amines, aromatic amines, and polycyclic hydrocarbons) and the alcohol metabolite acetaldehyde into carcinogens [22], which in turn may activate oncogenes. Our results indicate that subjects who smoke or consume alcohol, especially heavy smokers and heavy drinkers, had a significantly increased risk of laryngeal cancer. This further confirms that smoke and alcohol are risk factors for laryngeal cancer. Furthermore, in our study on the combined effects of gene polymorphisms and the environment on the risk of laryngeal cancer, we found that combined effects increased the risk of laryngeal cancer. However, Soucek et al. [23] found no synergistic effects of tobacco or alcohol with genetic factors regarding head and neck cancer. These analyses and data indicate that tobacco or alcohol and CYP1B1 polymorphisms are associated with the risk of laryngeal cancer. In addition, when the genetic factors are combined with the environmental factors, there are significant synergistic effects of tobacco or alcohol and CYP1B1 polymorphisms.

Conclusions

This study demonstrates that CYP1B1 gene polymorphism is closely associated with the risk of laryngeal cancer. Combined single-gene and multi-gene analyses further confirmed that the CYP1B1 rs1056827 mutant gene is a risk factor for laryngeal cancer, while the CYP1B1 rs1056836 mutant gene is a protective factor for laryngeal cancer. The risk of laryngeal cancer increases with an increased number of cancer risk alleles. Environmental factors (alcohol and tobacco) play a significant role in the incidence of laryngeal cancer. Exposure to alcohol and tobacco increases the risk of laryngeal cancer, and the combined effects of the environment and CYP1B1 gene polymorphism further increase the risk of laryngeal cancer.

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Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]