Genetic polymorphisms in the TERT-CLPTM1L region and lung cancer susceptibility in Chinese males

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Abstract. The objective of the present study was to analyze the relationship between genetic polymorphisms of the rs2736098 locus of the telomerase reverse transcriptase (TERT) gene and the rs401681 locus of the cleft lip and palate transmembrane protein 1 (CLPTM1L) gene and the risk of developing lung cancer in males in Jinzhou. A total of 214 lung cancer patients who were admitted in Jinzhou Medical University were analyzed, and 216 healthy males were selected as controls. Venous blood from all subjects and data on relevant risk factors were collected. DNA was extracted from peripheral blood by the phenol-chloroform method. Real-time fluorescent quantitative PCR (TaqMan real-time PCR) was used for DNA amplification. The genotyping results of the genetic polymorphisms of the TERT rs2736098 and CLPTM1L rs401681 loci were detected. The risk of developing lung cancer in the population with the TERT rs2736098 locus carrying the T allele was 1.614 times that with the TERT rs2736098 locus carrying the C allele after adjustment of the age factor. The risk of developing lung cancer in the population carrying the TT mutant genotype and the CT genotype increased significantly compared with that carrying the CC wild genotype \([\text{OR}=1.815, 95\% \ CI=1.132-2.957; \text{OR}=2.417, 95\% \ CI=1.158-4.943]\). Based on a comparison between the combination of the two mutant genotypes (CT+TT) and the wild homozygous genotype (CC), the mutant genotype increased the risk of developing lung cancer \((\text{OR}=0.553, 95\% \ CI=0.236-0.928)\). In conclusion, in males, the TERT rs2736098 and CLPTM1L rs401681 T alleles are the susceptibility factors for developing lung cancer. Individuals, including the smoking population, who carry both the TERT rs2736098 and CLPTM1L rs401681 T alleles are more likely to develop lung cancer.

Introduction

Tumorigenesis is a multi-factor, multi-stage, and multi-gene process. In addition to environmental factors, dietary factors, biological factors, and hereditary factors play important roles in tumor progression (1,2). Genetic susceptibility is determined by a single nucleotide on the individual genome (3,4). During tumorigenesis, environmental factors play an initiating role, while hereditary factors determine the susceptibility of individuals to tumorigenesis. In recent years, research on genetic susceptibility to tumors has attracted much attention. Recent research in molecular epidemiology has aimed to identify and determine the mutant loci of tumor-related genes, and further study the interactions between the environment and genes, and the interactions between genes by studying mononucleotide polymorphisms (4).

Within a DNA sequence, polymorphisms arising from mutation of a single nucleotide (A, T, C, and G) are called single nucleotide polymorphisms (SNPs) (5). SNPs are a major form of genome polymorphism (6). The gene coding region of an SNP is called a coding region SNP (cSNP), which may lead to changes in the amino acid sequence of proteins, and changes in protein function. cSNPs have important biological significance (7). Based on estimation, 1 in 1,000 people have one SNP in the genome. The 3 billion human basic groups have a total of over 3 million SNPs (8). Different individuals have different susceptibilities to carcinogenic factors in the environment because of polymorphisms. Therefore, SNPs can be used to screen populations susceptible to tumors in a rapid and large-scale manner. Research on SNPs related to tumors has also been a focus in molecular epidemiology in recent years. The chromosome 5p15.33 region has two known genes, human telomerase reverse transcriptase (TERT) and cleft lip and palate transmembrane protein 1 (CLPTM1L) (9-11). These genes have multiple cancer risk loci and may be associated with tumorigenesis.

TERT is the catalytic subunit of telomerase, and is located on chromosome 5p15.33. It spans 35 kb, and comprises 16 exons.
and 15 introns. It is a rate-limiting factor for synthesizing the telomerase holoenzyme (12). Its expression correlates with the expression of telomerase. Changes in TERT can also reflect corresponding changes in the activity of intracellular telomerase (13). TERT is an important target site for inhibiting telomerase activity. TERT can increase the risk of tumors by influencing telomerase activity and telomere length. In addition, telomerase participates in processes such as apoptosis, DNA damage repair, and regulation of gene expression, thus influencing tumorigenesis and progression (14,15).

The CLPTM1L gene encodes for a transmembrane protein, which induces apoptosis in cisplatin-resistant cell lines. It is expressed in multiple normal and malignant tissues such as the skin, lung, ovary, cervix, and thymus (16,17). However, the functions of CLPTM1L, and its role in tumorigenesis remain unclear. At present, CLPTM1L has been confirmed to be over-expressed in human ovarian tumor cell lines and is resistant to cisplatin. CLPTM1L overexpression in pulmonary tumor cells can protect them from apoptosis induced by genotoxic stress, indicating that it may have antiapoptotic function. CLPTM1L is also highly expressed in other tumor tissues. The aforementioned observations suggest that CLPTM1L may be associated with the genesis of multiple tumor types. The genome-wide association study reported that the SNPs, TERT rs2736098 and CLPTM1L rs401681, are significantly correlated with cancer risk (18).

Regarding research on the relationship between genetic polymorphisms of specific loci and lung cancer susceptibility, Zhang et al studied the relationship between the genetic polymorphism at rs2736098, and the risk of developing lung cancer in 400 lung cancer patients and 400 healthy subjects (controls) in the Asian population in 2012. Their results showed that genetic mutation at the rs2736098 locus increases the risk of developing lung cancer (19). Currently, there is no research on the relationship between the rs401681 locus and the risk of developing lung cancer.

Using a case-control design method, the aim of the present study was to analyze the relationship between the genetic polymorphism of the rs2736098 locus of the TERT gene and the rs401681 locus of the CLPTM1L gene and the risk of developing lung cancer in males in Jinzhou city.

Patients and methods

Selection of research subjects. Male patients definitely diagnosed with lung cancer based on histopathology who received operative treatment in Grade 3, Class A hospitals in Jinzhou city were selected, with a case-control research method, and assigned to the case group. Inclusion criteria for the case group: i) male; ii) primary lung cancer, excluding metastatic lung cancer and iii) received no chemotherapy or radioactive therapy. A total of 201 lung cancer patients aged from 30 to 87 years who sought medical advice in Grade 3, Class A hospitals in Jinzhou city from 2008 to 2013 were included as research subjects. In addition, 211 healthy males who underwent physical examinations in the physical examination center during the corresponding period were selected as controls using the frequency matching method. All research subjects signed an informed consent form. Next, blood samples from all research subjects were collected. Data on demographic characteristics, relevant clinical indexes, and exposure to environmental factors were obtained by questionnaires. This study was approved by the Ethics Committee of the First Affiliated Hospital of Jinzhou Medical University. Signed written informed consents were obtained from all participants before the study.

Epidemiological investigation. Uniformly prepared questionnaires were used. An epidemiological investigation into the research subjects was made by two trained investigators. The content of the investigation included demographic data (names and ages), smoking history, and clinical indexes. Non-smokers referred to individuals who smoked <100 cigarettes in their lives. The relevant clinical indexes were grouped according to the range of standard reference values. All investigation data were checked repeatedly and coded. A database was established with the EpiData software version 3.5 (Tree star Inc., Ashland, OR, USA), and data were entered.

DNA extraction. Frozen anticoagulated blood from lung cancer patients was thawed in a water bath at 37°C. A total of 1 ml of whole blood was taken, and 4 ml of erythrocyte lysis buffer (Sigma-Aldrich, St. Louis, MO, USA) was added. Samples were shaken sufficiently, mixed well, and allowed to stand for 30 min. Samples were centrifuged at 698.75 x g, and the supernatant was discarded. A total of 1 ml of the buffer + 11 ml protease K (Qiagen, Valencia, CA, USA) was added. Samples were inverted gently for 10 min, and centrifuged at 1,006.2 x g. The supernatant was pipetted into 5 ml EP tubes. This step was repeated once. An equal amount of 24:1 chloroform-isooamylol (Promega Corporation, Madison, WI, USA) was added. Samples were shaken gently for 10 min, and centrifuged at 1,006.2 x g. The supernatant was then pipetted. This step was repeated once. The supernatant was pipetted into 2 ml EP tubes. Cold anhydrous ethanol was added (Beijing Chemical Reagent Co., Ltd., Beijing, China). Samples were centrifuged at 10,500 x g for 10 min. The supernatant was discarded. A total of 200 ml of 70% ethanol was added. Samples were washed twice. Samples were then inverted slowly for 1 min, and centrifuged at 10,500 x g for 10 min. The supernatant was discarded. Samples were air dried at room temperature. A total of 100 ml of TE was added to dissolve the DNA. The OD value (Thermo Fisher Scientific, Waltham, MA, USA) was measured. Samples were placed at -20°C.

Real-time PCR genotyping. The TaqMan genotyping technique was used for the detection of TERT rs2736098 and CLPTM1L rs401681 polymorphisms. The PCR TaqMan probe and primers were designed and synthesized by ABI PE Applied Biosystems ( Foster City, CA, USA). TaqMan Master mix was from ABI PE Applied Biosystems. PCR reaction system: 2.50 µl of 2x TaqMan Master mix, 0.25 µl of 20x primer and probe mixture, 1.25 µl of H2O2, and 1.00 µl of DNA, for a total of 5.00 µl. PCR amplification conditions: PCR reactions and fluorescence signal reading were performed on an ABI 7500 fluorescent quantitation PCR amplifier (ABI PE Applied Biosystems). The amplification conditions were as
follows: pre-denaturation for 10 min at 95˚C; denaturation for 30 sec at 92˚C, annealing and extension for 1 min at 60˚C, for 47 cycles in total. SDS software version 4.0 (ABI PE Applied Biosystems) was used for genotype analysis. The genotypes of samples were judged by detecting FAM and VIC fluorescence intensity marked by different alleles of the same gene.

Statistical analysis. SPSS 19.0 software (SPSS, Inc., Chicago, IL, USA) was used for data analysis. A two-sided test was conducted to detect the differences in distribution of demographic characteristics, relevant risk factors, and SNP genotype between the case group and control group. P<0.05 was considered statistically significant. The logistic regression model was used to compute the odds ratio (OR) of various factors and their 95% confidence interval (95% CI), and analyze the relationship between genetic polymorphisms and the risk of developing lung cancer.

Results

General conditions of research subjects. The basic conditions of the case group and control group are shown in Table I. A total of 214 male lung cancer patients and 216 healthy males were included as research subjects. The ages of the case group and control group ranged from 30 to 86 years. The average age of the case group was 56.36±10.43 years, and the average age of the control group was 57.27±12.32 years. There were no significant differences in age between the two groups (P=0.513). Based on a statistical analysis, there were no significant differences in distribution of patients with or without a history of smoking between the case group and control group (P=0.256). The distribution of relevant clinical indexes of the lung cancer patients [carcinoembryonic antigen, tumor-node-metastasis (TNM) staging, lymphatic metastasis, and number of tumors] is shown in Table I.

Table I. Basic information on the case group and control group.

| Characteristics                  | Case group (%) | Control group (%) | P-value^a |
|----------------------------------|----------------|-------------------|-----------|
| Males                            | 214            | 216               |           |
| Average age                      | 56.36±10.43    | 57.27±12.32       | 0.513     |
| Smokers                          | 130 (60.7)     | 82 (34.1)         | 0.256     |
| Non-smokers                      | 84 (39.3)      | 134 (64.4)        |           |
| CRP                              | 161 (75.23)    |                   |           |
| SCCA (mg/l)                      | 56 (26.1)      |                   |           |
| CEA (mg/l)                       | 78 (36.4)      |                   |           |
| TNM stage I+II                   | 90 (42.0)      |                   |           |
| TNM stage III+IV                 | 124 (58.0)     |                   |           |
| No lymphatic metastasis          | 182 (85.0)     |                   |           |
| Lymphatic metastasis             | 32 (15.0)      |                   |           |
| No. of tumors                    |                |                   |           |
| =1                               | 105 (49.0)     |                   |           |
| ≥2                               | 99 (51.0)      |                   |           |

^aTwo-sided test; the differences were considered statistically significant when P<0.05. CRP, C-reactive protein; SCCA, squamous cell carcinoma antigen; CEA, carcinoembryonic antigen; TNM, tumor-node-metastasis.

Figure 1. Detection of the genotype of the TERT rs2736098 locus. The red points represent CC homozygous individuals. The blue points represent TT homozygous individuals. The green points represent CT heterozygous individuals. TERT, telomerase reverse transcriptase.
Relationship between the genetic polymorphisms of TERT and CLPTM1L and lung cancer susceptibility in males. The genotype frequencies of the two genetic loci, TERT rs2736098 and CLPTM1L rs401681, in both the case group and control group complied with Hardy-Weinberg equilibrium. The polymorphisms of the two genetic loci and the distribution of the alleles in both groups are shown in Table II. The results showed that the risk of developing lung cancer in the population with the TERT rs2736098 locus carrying the T allele was 1.614 times the risk of developing lung cancer in the population carrying the C allele (OR=1.614, 95% CI=1.134-2.267) following adjustment of the age factor. Furthermore, the risk of developing lung cancer in the population carrying the TT mutant gene and the CT genotype increased significantly compared with that in the population carrying the CC wild genotype. The differences were statistically significant (OR=1.815, 95% CI=1.132-2.957; OR=2.417, 95% CI=1.158-4.943). In addition, based on a comparison between the combination of two mutant genotypes (CT+TT) and the wild homozygous (CC) genotype, the mutant genotype increased the risk of developing lung cancer. The differences were statistically significant (OR=2.785, 95% CI=1.254-6.057). The results in Table IV show that individuals carrying the mutant genotypes (CT+TT), CC of TERT rs2736098, and mutant genotype (CT+TT) of CLPTM1L rs401681 in the smoking population had a significantly higher risk of developing lung cancer compared with those carrying the wild homozygous genotype (CC) in the non-smoking population (OR=2.348, 95% CI=1.156-4.347; OR=2.785, 95% CI=1.254-6.057). The differences were statistically significant.

Table II. Relationship between the genetic polymorphism of TERT and CLPTM1L and lung cancer susceptibility in males.

| Genotype | Case group | Control group | P-value | OR (95% CI) |
|----------|------------|---------------|---------|-------------|
| TERT rs2736098 | | | | |
| CC       | 78         | 123           |         | 1.0         |
| CT       | 95         | 77            | 0.013   | 1.815 (1.132-2.957) |
| TT       | 30         | 25            | 0.014   | 2.417 (1.158-4.943) |
| CT+TT    | 129        | 101           | 0.003   | 1.955 (1.121-3.157) |
| T allele |            |               |         | 1.614 (1.134-2.267) |
| CLPTM1L rs401681 | | | | |
| CC       | 85         | 128           |         | 1.0         |
| CT       | 99         | 79            | 0.015   | 1.732 (1.121-2.857) |
| TT       | 15         | 13            | 0.338   | 1.532 (0.651-3.546) |
| CT+TT    | 112        | 92            | 0.019   | 1.744 (1.151-2.736) |
| T allele |            |               |         | 1.343 (1.035-1.978) |

The OR value was subjected to age correction. The differences were considered statistically significant at P<0.05. TERT, telomerase reverse transcriptase; CLPTM1L, cleft lip and palate transmembrane protein 1; OR, odds ratio.

Table III. Relationship between the joint action of the genetic polymorphism of TERT and CLPTM1L and lung cancer susceptibility in males.

| TERT rs2736098 | CLPTM1L rs401681 | Case group | Control group | P-value | OR (95% CI) |
|----------------|------------------|------------|---------------|---------|-------------|
| CC             | CC               | 23         | 6             |         | 1.752 (0.944-3.267) |
| CC             | CT+TT            | 52         | 67            | 0.058   | 1.823 (1.177-3.236) |
| CT+TT          | CC               | 66         | 66            | 0.043   | 1.823 (1.177-3.236) |
| CT+TT          | CT+TT            | 63         | 30            | <0.001  | 4.457 (2.337-8.358) |

The OR value was subjected to age correction. The differences were considered statistically significant at P<0.05. TERT, telomerase reverse transcriptase; CLPTM1L, cleft lip and palate transmembrane protein 1; OR, odds ratio.
Analysis of the correlation between the genetic polymorphism of TERT and CLPTM1L and progression of lung cancer susceptibility in males.

| Smokers | Genotype | Case group | Control group | P-value | OR (95% CI) |
|---------|----------|------------|---------------|---------|-------------|
| TERT rs2736098 | CC | 38 | 65 | 1.0 |
| - | CT+TT | 47 | 72 | 0.543 | 1.255 (0.658-2.257) |
| + | CC | 25 | 41 | 0.755 | 0.815 (0.422-1.868) |
| + | CT+TT | 33 | 26 | 0.028 | 2.348 (1.156-4.347) |
| CLPTM1L rs401681 | CC | 36 | 73 | 1.0 |
| - | CT+TT | 45 | 61 | 0.159 | 1.533 (0.819-2.917) |
| + | CC | 25 | 43 | 0.816 | 1.048 (0.532-2.147) |
| + | CT+TT | 32 | 28 | 0.008 | 2.785 (1.254-6.057) |

*The OR value was subjected to age correction. The differences were considered statistically significant at P<0.05. TERT, telomerase reverse transcriptase; CLPTM1L, cleft lip and palate transmembrane protein 1; OR, odds ratio.

Table V. Analysis of the correlation between the genetic polymorphism of the TERT rs2736098 locus and the progression of course of disease of the male lung cancer patients.

| Genotype | I+II | III+IV | P-value | OR (95% CI) |
|----------|------|--------|---------|-------------|
| CC | 31 | 44 | 1.0 |
| CT | 53 | 45 | 0.547 | 0.144 (0.351-1.163) |
| TT | 12 | 18 | 0.768 | 0.644 (0.334-1.945) |
| CT+TT | 61 | 65 | 0.148 | 0.655 (0.348-1.219) |

Lymphatic metastasis (-)  Lymphatic metastasis (+)

| Genotype | I+II | III+IV | P-value | OR (95% CI) |
|----------|------|--------|---------|-------------|
| CC | 67 | 13 | 1.0 |
| CT | 89 | 10 | 0.558 | 0.256 (0.243-1.533) |
| TT | 28 | 5 | 0.947 | 0.919 (0.255-3.153) |
| CT+TT | 115 | 15 | 0.358 | 0.655 (0.259-1.519) |

One tumor  More than two tumors

| Genotype | I+II | III+IV | P-value | OR (95% CI) |
|----------|------|--------|---------|-------------|
| CC | 30 | 44 | 1.0 |
| CT | 56 | 44 | 0.543 | 0.047 (0.292-0.991) |
| TT | 17 | 12 | 0.435 | 0.058 (0.193-1.054) |
| CT+TT | 70 | 55 | 0.021 | 0.553 (0.236-0.928) |

*The OR value was subjected to age correction. The differences were considered statistically significant at P<0.05. TERT, telomerase reverse transcriptase; OR, odds ratio.

Discussion

The incidence of lung cancer is a multi-factor and multi-stage process caused by genetic and environmental factors. In recent years, numerous studies have focused on the
relationship between relevant genetic polymorphisms and lung cancer susceptibility. Studying males from Jinzhou city as research subjects, we investigated the relationship between the risk of developing lung cancer and polymorphisms of TERT and CLPTM1L as well as exposure to risk factors. Both SNPs at the TERT rs2736098 locus and CLPTM1L rs401681 locus can increase the risk of developing lung cancer. The interactions between the two factors and genetic and environmental factors significantly increase the risk of developing lung cancer.

TERT is the catalytic subunit of telomerase, and is located on chromosome 5p15.33. It spans 35 kb, and comprises 16 exons and 15 introns. It is a rate-limiting factor for synthesizing the telomerase holoenzyme. The rs2736098 locus is located on the second exon of the gene. The molecular weight of the TERT protein is approximately 127 kDa, and is primarily distributed in the nucleus. Mutation of its non-active structural domain, DAT, influences the binding between TERT and telomere DNA, thus affecting the activity of telomerase in extending telomeres. Moreover, it has higher tumor specificity (19).

Our results showed that there were significant differences in genotype frequencies between the case group and control group. The risk of developing lung cancer in the population carrying the T allele is increased significantly compared with the population carrying the C allele. The risk of developing lung cancer in the population carrying the mutant genotype and the CT genotype is increased significantly compared with the population carrying the CC wild genotype. The differences were statistically significant. These results indicate that genetic polymorphism of the TERT rs2736098 locus may be an independent risk factor for the incidence of lung cancer in males. CLPTM1L is located on the chromosome 5p15.33 region, and encodes for a transmembrane protein. It can induce cell apoptosis in cisplatin-resistant cell lines. It is expressed in multiple normal and malignant tissues such as the skin, lung, ovary, cervix, and thymus (20,21). Currently, CLPTM1L is confirmed to be overexpressed and resistant to cisplatin in human ovarian tumor cell lines. Its overexpression in pulmonary tumor cells can protect against apoptosis induced by genotoxic stress (22-24), indicating that it has anti-apoptotic function. However, the functions of CLPTM1L, and its role in tumorigenesis remain unclear. We studied the relationship between the genetic polymorphism of the CLPTM1L rs401681 locus and lung cancer in males. The risk of developing lung cancer in the population carrying the T allele is increased significantly compared with those carrying the C allele. Based on a comparison between the combination of the two mutant genotypes (CT+TT) and the wild homozygous genotype (CC), the mutant genotype increases the risk of developing lung cancer. There is no research on the relationship between the genetic polymorphism and lung cancer, whereas a great deal on lung cancer, but there are differences among the results.

This study had limitations. The sample-size was relatively small. The analysis only involved SNPs of two genes in the chromosome 5p15.33 region. Future studies require an expanded population range and increased sample-size. Furthermore, the analysis should involve multiple genetic loci. The relationship between genetic polymorphisms of the
rs2736098 and rs401681 loci and the progression of the disease requires further validation in future studies.

In conclusion, there is a correlation between genetic polymorphisms of TERT and CLPTM1L and lung cancer in males. The TERT rs2736098 and CLPTM1L rs401681T alleles increase the risk of developing lung cancer in males. They play a role in understanding the pathogenesis of lung cancer and screening for the high-risk population.

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