Genetic polymorphisms in the TERT gene and susceptibility to non-small cell lung cancer in a Chinese Han population

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Background: Recent studies have revealed that the TERT gene plays crucial roles in cancer initiation and development. Genome-wide analysis studies and case-control studies have demonstrated that polymorphisms in the TERT gene are associated with various cancers.

Materials and methods: In the current study, we analyzed the associations of eight single nucleotide polymorphisms (SNPs) in the TERT gene with non-small cell lung cancer (NSCLC) in a Chinese Han population. A total of 467 NSCLC patients and 526 healthy individuals were recruited for SNP genotyping using a TaqMan assay.

Results: Our results revealed that the allelic frequencies of rs2853677 and rs2853691 were significantly different between the NSCLC and control groups (P=0.004 and 0.001, respectively). Moreover, the T allele of rs2853677 and the A allele of rs2853691 might be the protective factors against NSCLC (OR=0.766; 95%CI: 0.639–0.918 and OR=0.714; 95%CI: 0.584–0.875, respectively). Additionally, stratified association analysis of the eight SNPs with different pathological NSCLC stages (I+II and III+IV) and different pathological types (adenocarcinoma and squamous cell carcinoma) revealed that none of the SNPs were significantly different between patients with different pathological stages and pathological types.

Conclusion: Our results indicated that rs2853677 and rs2853691 in the TERT gene might be associated with NSCLC in this Chinese Han population.

Keywords: TERT gene, polymorphisms, lung cancer, Chinese Han population

Introduction

Lung cancer is the most common cancer and is the leading cause of cancer death worldwide.1 Lung cancer can be subdivided into small cell lung cancer and non-small cell lung cancer (NSCLC). Despite the recent advances in early detection and treatment, the 5-year survival rate for lung cancer is below 15%, which indicates a poor prognosis.2 NSCLC accounts for more than 80% of lung cancers.3 Recently, studies have demonstrated that genetic factors, in addition to environmental factors, play important roles in the initiation and development of NSCLC. To date, genome-wide association studies (GWAS) have confirmed an underlying genetic contribution to lung cancer risk.4-6

Telomeres are sequences that cap the ends of chromosomes in eukaryotes and shorten with every successive mitotic cell division, which leads to replicative senescence. A minimal length of telomeric DNA is important for maintaining proper telomeric structure to protect chromosomes.7 However, gradual attrition has been found to occur in both proliferative and non-proliferative tissues as they age.8,9 This process is quintessential to the natural ageing process due to the limitations of telomerase, which...

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is essential for the maintenance of the telomere. However, the telomeres of cancer cells can be maintained throughout infinite division through telomerase-sustaining expression. In this manner, telomerase can promote tumor progression by ensuring the maintenance of telomeres above a critically short length to avoid cellular senescence and apoptosis.

Telomerase is an RNA-dependent DNA polymerase that is comprised of a catalytic subunit, which is encoded by the TERT gene, and an RNA component that is transcribed from the telomerase RNA component (TERC). Studies have identified the deregulation of telomerase as a hallmark of over 90% of human cancers that are associated with an upregulation of TERT. The upregulation of TERT expression has consistently been demonstrated to be one of the fundamental requirements for cellular transformation. The human TERT gene is located on 5p15.33 and consists of 16 exons and 15 introns that span over 40 kb in length. Studies have described mutations that can increase the transcriptional activity of the TERT gene promoter and thus may promote cancer progression. Moreover, genome-wide analysis studies and case-control studies have demonstrated that polymorphisms in the TERT gene are associated with various cancers, such as skin cancer, colorectal cancer, and breast cancer. In the current study, we investigated the associations of eight single nucleotide polymorphisms (SNPs) in the TERT gene with NSCLC in a Chinese Han population.

Materials and methods
Ethics statement
The protocols for the current study were in accordance with the Declaration of Helsinki and were approved by the Ethics Committees of the No.1 Affiliated Hospital of Kunming Medical University. All participants provided written informed consent.

Subjects
Four hundred and sixty-seven patients (315 males and 152 females) with NSCLC were recruited from the No.1 Affiliated Hospital of Kunming Medical University from July 2012 to May 2014. Subjects with oncotherapy histories, other cancers, hypertension, coronary heart disease, and diabetes were excluded from the current study. The pathological cancer stages were determined according to the International System for Staging Lung Cancer. In the current study, 73 patients were in stage I, 78 patients were in stage II, 165 patients were in stage III, and 151 patients were in stage IV. The histological type of NSCLC was identified according to the World Health Organization 2004 classifications. During the same time period, 526 healthy individuals (375 males and 151 females) were recruited from the same hospital from a routine health check-up population. The clinical characteristics, including gender, age, and histological types of lung cancer, were collected. Because the subjects with a family history of cancer were excluded from the control group, individuals with a family history of cancer were also excluded from the NSCLC group. All participants self-reported as Han and lived roughly within the Yunnan Province of Southwest China.

SNP selection and genotyping
In the current study, we selected eight SNPs (rs2736098, rs2853676, rs2853677, rs10069690, rs2075786, rs2736114, rs2736122, and rs2853691) in the TERT gene from the reports focusing on the association studies of polymorphisms in TERT gene through searching PubMed; SNPs with a minor allele frequency higher than 5% in Chinese population were included according to the 1000 genome data. SNP rs2736098 is located in exon 2, rs2853676 and rs2853677 are located in intron 2, rs10069690 is located in intron 4, rs2075786 and rs2736114 are located in intron 10, rs2736122 is located in intron 13, and rs2853691 is located in the near gene-3 region. Five milliliters of the whole blood of each subject were extracted. Next, the genomic DNA was extracted from the peripheral lymphocytes using the QIAamp Blood Mini Kit (Qiagen NV, Venlo, the Netherlands). The eight SNPs in the TERT gene were selected and genotyped using TaqMan assays. The TaqMan assays (primers and probes) were designed and produced by Thermo Fisher Scientific (Waltham, MA, USA). The assay ID for each of the SNPs was as follows: rs2075786 (C__15824034_10), rs2736114 (C__1844035_20), rs10069690 (C__30322061_10), rs2736098 (C__26414916_20), rs2736122 (C__1844039_10), rs2853676 (C__8773291_20), rs2853677 (C__1844008_10), and rs2853691 (C__1844041_10). A 5 μL reaction system comprised of 2.5 μL 2 × TaqMan Master Mix, 0.125 μL 40 × primer and TaqMan Probe (FAM VIC) dye mix, 1.375 μL ddH₂O, and 1 μL template DNA (substituted with the equivalent ddH₂O volume in the negative controls) was ampliﬁed in a 384-well plate using the following PCR cycle conditions: 95°C for 10 min; and a PCR stage at 92°C for 10s and 60°C for 1 min, repeated for 40 cycles. The data acquisition was performed using a QuantStudio 6 Flex Fast Real-Time PCR system, and the data were further analyzed with the QuantStudioReal-time PCR software (Thermo Fisher Scientific). Samples with each genotype of the eight SNPs were sequenced to evaluate the accuracy of the SNP genotyping using the TaqMan assay.
Statistical analysis
The statistical analyses were conducted using Microsoft Excel software and the SPSS 19.0 statistical package (IBM Corporation, Armonk, NY, USA). The Hardy-Weinberg equilibrium (HWE) was tested to evaluate the representativeness of the NSCLC and control groups. The effects of the polymorphisms on the risk of NSCLC are expressed as ORs with the 95% CIs, which were calculated using logistic regression analysis with adjustments for age and gender. The linkage equilibrium (LD) and haplotype frequencies were calculated based on the genotyping results using the expectation-maximization algorithm of the SHEsis software.\(^{26,27}\) A \(D^*\) value >0.8 indicated the existence of different loci in the LD. The differences in the haplotypes between the case and control groups were determined with \(\chi^2\) tests with Bonferroni corrections for multiple testing. The association of each genotype with the risk of NSCLC was evaluated using the inheritance model analysis of the SNPstats software.\(^{24}\) The following five inheritance models were analyzed: codominant, dominant, recessive, overdominant, and log-additive.\(^{28}\) The Akaike information criterion (AIC) and Bayesian information criterion (BIC) were calculated to determine the best fit model for each SNP. The sample size and the statistical power was calculated using “Power and Sample Size” program.\(^{29}\) Bonferroni corrections were applied to correct for multiple comparisons, and the threshold for statistical significance was set at \(P<0.05/n\).

Results
Subject characteristics
The clinical characteristics of the subjects are presented in Table 1. Neither age nor gender differed significantly between the NSCLC and control groups \((P>0.05)\). There were 285 NSCLC patients with adenocarcinomas (ACs), 172 patients with squamous cell carcinomas (SCCs), and ten patients with ACs and SCCs (AC+SCC). Seventy-three patients were in stage I, 78 patients were in stage II, 165 patients were in stage III, and 151 patients were in stage IV.

| Characteristics                  | NSCLC  | Control | \(P\)-value |
|----------------------------------|--------|---------|-------------|
| \(N\)                            | 467    | 526     |             |
| Age (years)                      | 56.02±10.76 | 54.94±9.45 | 0.095       |
| Gender (M/F)                     | 315/152 | 375/151 | 0.191       |
| Adenocarcinoma                   | 285    |         |             |
| Squamous cell carcinoma          | 172    |         |             |
| Adenocarcinoma and squamous cell carcinoma | 10    |         |             |
| Clinical stage                   |        |         |             |
| I                                | 73     |         |             |
| II                               | 78     |         |             |
| III                              | 165    |         |             |
| IV                               | 151    |         |             |

**Table 1** Clinical characteristics of the subjects enrolled in the present study

LD and haplotype analysis of the eight SNPs in the TERT gene
Table 5 lists the linkage relationship of the SNPs. The LD values \((D^*)\) between rs2853676 and rs2853677, and between rs2075786, 2736114, and 2736122 were all over 0.800. According to the LD results, we constructed the haplotypes

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of the SNPs between which the LD values were significant ($D' > 0.800$) and analyzed the differences in the haplotype frequencies (frequencies greater than 3%) between the NSCLC and control groups. The results revealed that the haplotype frequencies of the rs2853676C-rs2853677T and rs2853676C-rs2853677C SNPs significantly differed between the NSCLC and control groups ($P = 0.004$ and $0.009$, respectively) after Bonferroni correction ($P < 0.017$). However, the haplotype frequencies of the rs2075786A-rs2736114G-rs2736122G, rs2075786G-rs2736114C-rs2736122G, and rs2075786G-rs2736114T-rs2736122A were not significantly different between the NSCLC and control groups ($P > 0.017$) (Table 6).

### Association analysis of eight SNPs in the TERT gene with different NSCLC pathological stages

Table 7 presents the distributions of the genotypes and alleles of the eight SNPs in the different NSCLC pathological stages (i.e., I+II and III+IV). A logistic regression analysis revealed

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**Table 2** The association analysis between the eight SNPs in TERT gene and NSCLC (after adjusting for gender and age)

| SNPs          | Genotypes (n, %) | $\chi^2$ | P-value | Alleles (n, %) | $\chi^2$ | P-value* | OR (95% CI) |
|---------------|------------------|---------|---------|----------------|---------|---------|-------------|
| rs2736098     | C/C            | 167 (0.358) | 0.610   | 0.737          | 568 (0.608) | 0.562   | 0.445 (0.777–1.117) |
|               | C/T            | 234 (0.501) | 66 (0.141) |               | 366 (0.392) | 395 (0.375) |             |
| NSCLC         | T/T            | 67 (0.127)   |         |               | C      | T      |             |
| Control       |                 |           |         |               |         |         |             |
| rs2853676     | C/C            | 312 (0.668) | 0.361   | 0.835          | 757 (0.810) | 0.385   | 0.563 (0.744–1.174) |
|               | C/T            | 133 (0.285) | 22 (0.047) |               | 177 (0.190) | 0.385   | 0.935 (0.744–1.174) |
| NSCLC         | T/T            | 44 (0.094)   | 22 (0.042) |               | 188 (0.179) | 0.385   |             |
| Control       |                 |           |         |               |         |         |             |
| rs2853677     | T/T            | 143 (0.306) | 9.204   | 0.010          | 532 (0.570) | 8.587   | 0.004 (0.639–0.918) |
|               | C/C            | 246 (0.527) | 78 (0.167) |               | 402 (0.430) | 8.587   |             |
| NSCLC         | T/T            | 16 (0.034)   | 15 (0.029) |               | 186 (0.199) | 0.003   |             |
| Control       |                 |           |         |               |         |         |             |
| rs10069690    | A/A            | 203 (0.386) | 1.070   | 0.586          | 748 (0.801) | 1.070   | 0.980 (0.803–1.252) |
|               | A/G            | 261 (0.496) | 62 (0.118) |               | 184 (0.198) | 1.070   |             |
| NSCLC         | C/C            | 78 (0.152)   | 15 (0.029) |               | 208 (0.219) | 1.070   |             |
| Control       |                 |           |         |               |         |         |             |
| rs2736098     | C/C            | 322 (0.632) | 0.017   | 0.991          | 748 (0.801) | 0.017   | 0.766 (0.639–0.918) |
|               | C/T            | 178 (0.339) | 16 (0.034) |               | 186 (0.199) | 0.017   |             |
| NSCLC         | T/T            | 78 (0.152)   | 15 (0.029) |               | 208 (0.219) | 0.017   |             |
| Control       |                 |           |         |               |         |         |             |
| rs2736114     | C/C            | 319 (0.683) | 0.017   | 0.991          | 748 (0.801) | 0.017   | 0.766 (0.639–0.918) |
|               | C/T            | 163 (0.310) | 20 (0.038) |               | 203 (0.213) | 0.017   |             |
| NSCLC         | T/T            | 16 (0.034)   | 15 (0.029) |               | 208 (0.219) | 0.017   |             |
| Control       |                 |           |         |               |         |         |             |

Note: *Statistically significant threshold was set at $P < 0.006$ (0.05/n, $n = 8$) determined by Bonferroni correction.

Abbreviations: SNPs, single nucleotide polymorphisms; NSCLC, non-small cell lung cancer.

**Table 3** Different inheritance model analysis of rs2853677 in TERT gene between NSCLC and control groups (after adjusting for gender and age)

| Models        | Genotypes | NSCLC (n, %) | Control (n, %) | OR (95% CI) | P-value* |
|---------------|-----------|--------------|---------------|-------------|----------|
|               |           |              |               |             | AIC      | BIC      |
| Codominant    | T/T       | 143 (30.6%)  | 203 (38.6%)   | 1           | 0.011    | 1369.2   | 1393.7   |
|               | T/C       | 246 (52.7%)  | 261 (49.6%)   | 0.74 (0.56–0.98) |         |         |         |         |
|               | C/C       | 78 (16.7%)   | 62 (11.8%)    | 0.57 (0.38–0.84) |         |         |         |         |
|               |           |              |               |             |         |         |         |         |
| Dominant      | T/T       | 143 (30.6%)  | 203 (38.6%)   | 1           | 0.008    | 1369.1   | 1388.7   |
|               | T/C       | 324 (69.4%)  | 323 (61.4%)   | 0.70 (0.54–0.91) |         |         |         |         |
|               | C/C       | 58 (12.4%)   | 404 (74.6%)   | 0.68 (0.54–0.91) |         |         |         |         |
|               |           |              |               |             |         |         |         |         |
| Recessive     | T/T       | 221 (47.3%)  | 225 (50.4%)   | 1           | 0.035    | 1371.8   | 1391.4   |
|               | T/C       | 452 (83.3%)  | 464 (88.2%)   | 0.87 (0.68–1.12) |         |         |         |         |
|               | C/C       | 78 (16.7%)   | 62 (11.8%)    | 0.68 (0.47–0.97) |         |         |         |         |
|               |           |              |               |             |         |         |         |         |
| Overdominant  | T/T       | 221 (47.3%)  | 225 (50.4%)   | 1           | 0.280    | 1375.1   | 1394.7   |
|               | T/C       | 452 (83.3%)  | 464 (88.2%)   | 0.87 (0.68–1.12) |         |         |         |         |
|               | C/C       | 78 (16.7%)   | 62 (11.8%)    | 0.68 (0.47–0.97) |         |         |         |         |
|               |           |              |               |             |         |         |         |         |
| Log-additive  | —         | —            | —             | 0.75 (0.62–0.91) | 0.003    | 1367.2   | 1386.8   |

Note: *Statistically significant threshold was set at $P < 0.006$ (0.05/n, $n = 8$) determined by Bonferroni correction.

Abbreviations: NSCLC, non-small cell lung cancer; AIC, Akaike information criterion; BIC, Bayesian information criterion.
that the genotypic and allelic frequencies of the eight SNPs did not significantly differ between I+II and III+IV NSCLC pathological stages after Bonferroni correction ($P > 0.006$).

### Association analysis of eight SNPs in the TERT gene with different NSCLC pathological types (AC and SCC)

Table 8 presents the results of the association between the eight SNPs and different NSCLC pathological types (AC and SCC). The logistic regression analysis revealed that the genotypic and allelic distributions of the eight SNPs were not significantly different between AC and SCC.

### Discussion

The progression, growth, and metastasis of tumor cells require both increased angiogenesis and increased proliferation, and these processes both depend on the maintenance of telomeres via the sustained activation of telomerase. Telomerase activity is dependent on several factors, among which the catalytic component TERT acts as a determinant of telomerase activity. Although the transcription of TERT is repressed in most somatic cells, the increased expression of TERT has been demonstrated to be a fundamental requirement of cellular transformation.

Recently, polymorphisms in the TERT gene promoter were demonstrated to increase TERT transcription activity.
Given the crucial role of TERT in the activation of telomerase, polymorphisms in the TERT gene might be associated with cancers via their effects on the expression of TERT. In addition to this SNP, in the current study, we investigated the associations of seven other SNPs (i.e., rs2075786, rs2736114, rs10069690, rs2736098, rs2736122, rs2853676, rs2853677, and rs2853691) in the TERT gene with NSCLC in a Chinese Han population. Our results showed that rs2853677 located in intron 2 and rs2853691 located near the 3’ region of the TERT gene might be associated with NSCLC in the Chinese Han population in the current study.

In 2016, Zhou et al reported that rs2853691 in the TERT gene was associated with esophageal squamous cell carcinoma (ESCC), and they found that the A allele of rs2853691 was the protective factor of ESCC. In the current study, we also found that rs2853691 was associated with NSCLC susceptibility, and the A allele of rs2853691 was the protective factor of NSCLC in the Chinese Han population. In 2010, Atzmon et al found that this SNP is associated with telomere length in Ashkenazi centenarians. However, in 2012, Soerensen et al reported no association between SNPs in TERT and telomere length in longevity population of the Danish population. The differences might be due to the specific population. Although this association has not been verified in Chinese or cancer patients, rs2853691 could be associated with NSCLC in the current population through affecting telomere length. In the future, the exploitation of this information for its applicability to assessments of lung cancer susceptibility will require additional associational and functional studies.

If a polymorphism is located in a promoter region, protein-coding region or a 3’ UTR region, that polymorphism might affect cancer susceptibility by affecting gene transcription, altering protein function or regulating protein yield. However, rs2853677 is located in the second intron at +7969 base pairs from the transcription start site of the TERT gene. Interestingly, GWAS have identified rs2853677 as a susceptibility locus for lung cancer in Japanese and African-American populations. In 2015, Campa et al demonstrated that rs2853677 is associated with pancreatic cancer susceptibility. Moreover, this SNP has been identified as being associated with myeloproliferative neoplasms in another study.

Table 7 The association analysis between the eight SNPs in TERT and NSCLC pathological stages I+II and III+IV (after adjusting for gender and age).

| SNPs          | Genotypes (n, %) | χ²   | P-value* | Alleles (n, %) | χ²   | P-valuea | OR (95% CI) |
|---------------|------------------|------|----------|----------------|------|----------|-------------|
| rs2736098     | C/C (110)        |       |          |                |      |          |             |
|               | C/T (162)        |       | 0.349    | 0.764          |      | 0.382    | 0.869 (0.635–1.190) |
|               | T/T (44)         |       | 0.139    |                |      | 0.322    |             |
| rs2853676     | C/C (205)        |       |          |                |      |          |             |
|               | C/T (94)         |       | 0.297    | 0.363          |      | 0.131    | 0.729 (0.483–1.099) |
|               | T/T (17)         |       | 0.054    |                |      | 0.006    |             |
| rs2853677     | T/T (95)         |       |          |                |      |          |             |
|               | T/C (165)        |       | 0.522    | 0.688          |      | 0.154    | 0.797 (0.584–1.088) |
|               | C/C (56)         |       | 0.177    |                |      | 0.052    |             |
| rs2075786     | A/A (193)        |       |          |                |      |          |             |
|               | A/G (112)        |       | 0.354    | 0.265          |      | 0.118    | 0.724 (0.483–1.085) |
|               | G/G (11)         |       | 0.035    |                |      | 0.006    |             |
| rs2736114     | C/C (110)        |       |          |                |      |          |             |
|               | C/T (38)         |       | 0.252    | 0.249          |      | 0.150    | 0.731 (0.478–1.119) |
|               | T/T (3)          |       | 0.020    |                |      | 0.012    |             |
| rs2736122     | A/A (276)        |       |          |                |      |          |             |
|               | A/G (38)         |       | 0.120    | 0.247          |      | 0.153    | 0.570 (0.264–1.231) |
|               | G/G (2)          |       | 0.006    |                |      | 0.000    |             |
| rs2853691     | A/A (139)        |       |          |                |      |          |             |
|               | A/G (12)         |       | 0.079    | 0.247          |      | 0.153    | 0.570 (0.264–1.231) |
|               | G/G (13)         |       | 0.000    |                |      | 0.000    |             |
| rs2736114     | I+II (166)       |       |          |                |      |          |             |
|               | C/C (121)        |       | 0.383    | 0.648          |      | 0.445    | 1.137 (0.818–1.581) |
|               | C/T (29)         |       | 0.092    |                |      | 0.052    |             |
|               | T/T (18)         |       | 0.119    |                |      | 0.038    |             |

Note: *Statistically significant threshold was set at P<0.006 (0.05/n, n=8) determined by Bonferroni correction.
Abbreviations: SNPs, single nucleotide polymorphisms; NSCLC, non-small cell lung cancer.
that the T allele of rs2853677 was a protective factor against NSCLC susceptibility in a Chinese Han population, which is consistent with the findings of previous studies. In 2016, a study by Li et al indicated that rs2853677 is located in a functional enhancer region of the gene, which indicates that rs2853677 affects the transcription of TERT by altering the binding affinity of a transcription factor. These data demonstrate that rs2853677 in the TERT gene might play an important role in lung cancer via its effects on the transcription of TERT.

In 2015, Zhang et al found that the C allele of rs2736098 was associated with an increased risk of gastrointestinal stromal tumor. However, in the current study, rs2736098 exhibited no association with NSCLC in a Chinese Han population, and this finding is consistent with those of a study of hepatocellular carcinomas by Yuan et al. Moreover, the results related to rs2853676, rs10069690, rs2075786, and rs2736122 have exhibited inconsistencies in different studies (including the current study). The reasons for these inconsistencies could be related to the different diseases studied and different genetic backgrounds of the studied populations. In the current study, we also investigated the associations of these SNPs with the different pathological stages and types. However, the results revealed that none of the SNPs were associated with the pathological stages and types of NSCLC in the current population.

**Conclusion**

Studies have demonstrated that TERT might play a special role in cancer development and could represent another molecular target for cancer diagnosis and/or therapy. In the current study, we observed that the T allele of rs2853677 and the A allele of rs2853691 in the TERT gene might be protective factors against NSCLC in a Chinese Han population. The statistical power of rs2853677 and rs285369 were 0.815 and 0.898 calculated by “Power and Sample Size” program. However, one limitation that might have affected the results of the association study was the lack of smoking status data of the control individuals. This limitation made it difficult to perform a gene-smoking interaction analysis in the current study. In the future, larger scale samples and systemic reviews would be helpful for clarifying the associations of the variations in the TERT gene with NSCLC. Moreover, further combining the functional research would promote the diagnostic and therapeutic applications of targeting the TERT gene in NSCLC.

**Table 8** The association analysis between the eight SNPs in TERT and NSCLC different pathological types (after adjusting for gender and age)

| SNPs            | Genotypes (n, %) | χ² | P-value | Genotypes (n, %) | χ² | P-value | OR (95% CI) |
|-----------------|-----------------|----|---------|-----------------|----|---------|-------------|
| rs2736098       | C/C             |    |         | T/T             |    |         |             |
| AC              | 110 (0.386)     |    |         | 45 (0.158)      |    |         |             |
| SCC             | 55 (0.320)      |    |         | 19 (0.110)      |    |         |             |
| rs2853676       | C/C             |    |         | T/T             |    |         |             |
| AC              | 191 (0.670)     |    |         | 17 (0.060)      |    |         |             |
| SCC             | 112 (0.651)     |    |         | 5 (0.029)       |    |         |             |
| rs2853677       | T/T             |    |         | C/C             |    |         |             |
| AC              | 86 (0.302)      |    |         | 55 (0.193)      |    |         |             |
| SCC             | 55 (0.320)      |    |         | 21 (0.122)      |    |         |             |
| rs10069690      | C/C             |    |         | T/T             |    |         |             |
| AC              | 181 (0.635)     |    |         | 6 (0.021)       |    |         |             |
| SCC             | 105 (0.610)     |    |         | 7 (0.041)       |    |         |             |
| rs2075786       | A/A             |    |         | G/G             |    |         |             |
| AC              | 196 (0.688)     |    |         | 12 (0.042)      |    |         |             |
| SCC             | 116 (0.674)     |    |         | 4 (0.023)       |    |         |             |
| rs2736114       | C/C             |    |         | T/T             |    |         |             |
| AC              | 256 (0.898)     |    |         | 1 (0.004)       |    |         |             |
| SCC             | 150 (0.872)     |    |         | 1 (0.006)       |    |         |             |
| rs2736122       | A/A             |    |         | G/G             |    |         |             |
| AC              | 1 (0.004)       |    |         | 249 (0.874)     |    |         |             |
| SCC             | 4 (0.023)       |    |         | 147 (0.855)     |    |         |             |
| rs2853691       | A/A             |    |         | G/G             |    |         |             |
| AC              | 155 (0.544)     |    |         | 29 (0.102)      |    |         |             |
| SCC             | 82 (0.477)      |    |         | 17 (0.099)      |    |         |             |

Note: *Statistically significant threshold was set at P<0.006 (0.05/n, n=8) determined by Bonferroni correction.

Abbreviations: SNPs, single nucleotide polymorphisms; NSCLC, non-small cell lung cancer.
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Disclosure

The authors report no conflicts of interest in this work.

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