Introduction

Reversible phosphorylation of proteins is an important regulatory mechanism for maintaining cell homeostasis that regulates cell growth, proliferation, apoptosis, survival and differentiation [1]. It balances phosphorylation-dependent signal transduction pathways by virtue of the phosphorylation with protein kinases and dephosphorylation with protein phosphatases. Multiple evidences have indicated that the aberrant activity of phosphorylation involves the development of several cancers (e.g., lung cancer), which was caused by activated oncogenic kinases and inactivated phosphatases [2]. Inactivated phosphatases would lead to aberrant response manner (P_{onens} = 5.63 \times 10^{-6}) of the two variants, the number of the adverse genotypes was positively associated with lung cancer risk in a dose-response manner (P_{trend} = 5.63 \times 10^{-6}). Further functional assay showed that lung cancer tissues carrying rs1255722AA variant genotype had a significantly lower mRNA level of PPP2R5E compared with tissues carrying GG/AA genotypes. However, such effect was not observed for the other SNPs and other combinations. Our findings suggested that the two functional variants in PPP2R1A and PPP2R5E and their combination are associated with lung cancer risk in Chinese, which may be valuable biomarkers to predict risk of lung cancer.

Abstract

Protein phosphatase-2A (PP2A) is one of the major cellular serine-threonine phosphatases and functions as a tumor suppressor that negatively regulates the activity of some oncogenic kinases. Recent studies have reported that PP2A expression was suppressed during lung carcinogenesis, we therefore hypothesized that the single nucleotide polymorphisms (SNPs) in PP2A subunit genes may affect PP2A function and thus contribute to lung cancer susceptibility. In a two-stage case-control study with a total of 1559 lung cancer patients and 1679 controls, we genotyped eight putative functional SNPs and one identified functional SNP (i.e., rs11453459) in seven major PP2A subunits (i.e., PPP2R1A, PPP2R1B, PPP2CA, PPP2R2A, PPP2R2B, PPP2R5C, PPP2R5E) in southern and eastern Chinese. We found that rs11453459G (+G/GG) variant genotypes of PPP2R1A and the rs1255722AA variant genotype of PPP2R5E conferred increased risks of lung cancer (rs11453459, -G/GG vs. +: OR = 1.31, 95% CI = 1.13–1.51; rs1255722, AA vs. AG/GG: OR = 1.27, 95% CI = 1.07–1.51). After combined the two variants, the number of the adverse genotypes was positively associated with lung cancer risk in a dose-
cancer [20–22]. Remarkably, the results from one genome-wide association study (GWAS) conducted in Chinese, in which we previously participated, identified a intron single nucleotide polymorphism (SNP) near one B regulatory subunit (PPP2R2B) to be a lung cancer susceptible locus, reflecting an important role of in PP2A on lung cancer susceptibility [23]. However, no study has yet systematically tested the associations between genetic variants in PP2A subunit genes and lung cancer risk. Therefore, in current study, we tested the hypothesis that the genetic variants in PP2A subunit genes may alter the susceptibility of lung cancer.

Because the PP2A has tissue-expressed specificity, we selected genetic variants of these PP2A subunits with function in lung based on previous published articles (i.e., PPP2R1A [24], PPP2R1B [25], PPP2R5A [26], PPP2R2A [27], PPP2R2B [23], PPP2R5C [28] and PPP2R5E [29]). In a two-stage case-control study, we genotyped nine putative functional SNPs of above genes in southern Chinese and validated the promising SNPs in eastern Chinese to analyze the associations between them and lung cancer risk. The effect of promising SNPs on gene expression was further detected.

### Materials and Methods

#### Study subjects

In this study, two independent case-control samplings including a southern Chinese population as a discovery set and an eastern Chinese population as a validation set were used as previously described [30–34]. In brief, there were 1056 histopathologically confirmed primary lung cancer cases and 503 newly diagnosed lung cancer patients and 623 age (±5 years) and sex frequency-matched healthy controls in the validation set. All the participants were genetically-unrelated ethnic Han Chinese and none had blood transfusion in the last 6 months. Having given a written informed consent, each participant was scheduled for an interview with a structured questionnaire to collect selected information, and to donate 5ml peripheral blood. The definition of smoking status, pack-years smoked, drink status and family history of cancer have been described previously [32,35]. The study was approved by the institutional review boards of Guangzhou Medical University and Soochow University.

#### SNP selection

By searching the dbSNP database (http://www.ncbi.nlm.nih.gov/), we found there were nine putative functional SNPs in the aforementioned seven genes which are located in the predicted 2000 bp promoter, coding region and 3’-untranslated region (3’-UTR) with minor allele frequency (MAF) >0.5% in Han Chinese. They are rs1334984T>C in promoter, rs10421191G>A in 3’-UTR of PPP2R1A, rs2850247 C>A and rs612345 A>G in promoter of PPP2R2B, rs7840553G>T in promoter of PPP2R2A, rs3742424G>C in coding region of PPP2R5C (causing an amino acid change from Alanine to Proline at codon 476), rs1255720A in promoter of PPP2R5E, rs2992283G>A in promoter of PPP2R1A. The linkage disequilibrium (LD) analysis further showed that the two SNPs (rs1255720T>C and rs1255722G>A) of PPP2R5F were in completely LD with each other ($r^2 = 0.309$, $D’ = 1.0$), we therefore selected one of them.

#### Table 1. Associations between the SNPs in candidate PP2A subunits and risk of lung cancer in the discovery set.

| SNP        | Gene, location | Case | Control | MAF | OR_{het} | OR_{hom} | Trend test | OR (95%CI) |
|------------|---------------|------|---------|-----|----------|----------|------------|------------|
| rs1334984T >C | PPP2R1A, promoter | 849/193/9 | 846/190/15 | 0.100 | 1.01 (0.81–1.27) | 0.63 (0.27–1.44) | 0.699 (0.79–1.17) | 0.96 |
| rs11453459 >G | PPP2R1A, promoter | 582/392/68 | 656/342/52 | 0.253 | 0.212 | 1.29 (1.08–1.56) | 1.51 (1.04–2.22) | 0.002 (1.11–1.58) |
| rs10421191G >A | PPP2R1A, 3’-UTR | 658/322/68 | 639/342/63 | 0.319 | 0.224 | 0.91 (0.76–1.10) | 1.03 (0.72–1.47) | 0.620 (0.78–1.11) |
| rs2850247C >A | PPP2R1B, promoter | 805/233/10 | 823/209/10 | 0.121 | 0.110 | 1.14 (0.92–1.41) | 1.08 (0.45–2.61) | 0.252 (0.92–1.40) |
| rs612345A >G | PPP2R1B, promoter | 628/378/46 | 599/397/54 | 0.223 | 0.241 | 0.92 (0.77–1.10) | 0.82 (0.54–1.23) | 0.222 (0.79–1.06) |
| rs7840855C >T | PPP2R2A, promoter | 690/343/12 | 727/305/20 | 0.176 | 0.164 | 1.18 (0.98–1.42) | 0.64 (0.31–1.32) | 0.312 (0.95–1.38) |
| rs3742424G >C | PPP2R5C, coding | 560/406/86 | 555/433/66 | 0.275 | 0.268 | 0.94 (0.78–1.12) | 1.30 (0.92–1.83) | 0.564 (0.83–1.17) |
| rs1255722G >A | PPP2R5E, promoter | 292/530/231 | 330/531/191 | 0.471 | 0.434 | 1.13 (0.93–1.38) | 1.38 (1.07–1.77) | 0.013 (1.02–1.57) |
| rs2292283G >A | PPP2CA, promoter | 349/518/178 | 353/504/187 | 0.418 | 0.421 | 1.05 (0.88–1.28) | 0.97 (0.75–1.25) | 0.951 (0.88–1.24) |

**Abbreviation:** MAF, minor allele frequency; OR_{het}, heterozygote versus wild-genotype homozygote; OR_{hom}, variant homozygote versus wild-type homozygote; 3’-UTR, 3’-untranslated region.

*a*Wild-type homozygote/heterozygote/variant homozygote.

*b*The observed genotype frequencies among the controls were all in agreement with the Hardy-Weinberg equilibrium in the control subjects.

*c*Wild-type homozygote/heterozygote/variant homozygote.

*d*Data were calculated by unconditional logistic regression, adjusted for age, sex, smoking status, drinking status and family history of cancer.

*e*OR and 95%CI was calculated based on the bested genetic model.

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Table 2. Frequency distribution of the SNP rs11453459->G and rs1255722G ->A and their associations with lung cancer risk.

| Genotypes/alleles | Validation set | Merged set |
|-------------------|----------------|------------|
|                   | Case n (%)     | Control n (%) | Adjusted OR(95% CI) | Case n (%)     | Control n (%) | Adjusted OR(95% CI) |
| rs11453459->G     |                |             |                     |                |             |                     |
| -                 | 288 (57.6)     | 393 (63.5)  | 1.00 (ref)          | 870 (56.4)     | 1049 (62.9)  | 1.00 (ref)          |
| +G                | 183 (36.6)     | 201 (32.5)  | 1.25 (0.96–1.61)    | 575 (37.3)     | 543 (32.5)    | 1.28 (1.10–1.48)    |
| GG                | 29 (5.8)       | 25 (4.0)    | 1.53 (0.87–2.70)    | 97 (6.3)       | 77 (4.6)      | 1.53 (1.12–2.09)    |
| Trend test P value |               |             |                     |               |             |                     |
| G allele          | 0.241          | 0.203       |                     | 0.249          | 0.209        |                     |
| Dominant model    |               |             |                     |                |             |                     |
| -                 | 288 (57.6)     | 393 (63.5)  | 1.00 (ref)          | 870 (56.4)     | 1049 (62.9)  | 1.00 (ref)          |
| G (+G + GG)       | 212 (42.4)     | 226 (36.5)  | 1.28 (1.00–1.63)    | 672 (43.6)     | 620 (37.1)    | 1.31 (1.13–1.51)    |
| rs1255722G ->A    |                |             |                     |                |             |                     |
| GG                | 146 (29.1)     | 182 (29.2)  | 1.00 (ref)          | 438 (28.2)     | 512 (30.6)    | 1.00 (ref)          |
| AG                | 245 (48.9)     | 325 (52.2)  | 0.95 (0.72–1.25)    | 775 (49.9)     | 856 (51.1)    | 1.06 (0.91–1.25)    |
| AA                | 110 (22.0)     | 116 (18.6)  | 1.25 (0.88–1.77)    | 341 (21.9)     | 307 (18.3)    | 1.32 (1.08–1.61)    |
| Trend test P value |               |             |                     | 0.276          |             |                     |
| A allele          | 0.464          | 0.447       |                     | 0.469          | 0.439        |                     |
| Recessive model   |               |             |                     |                |             |                     |
| AG + GG           | 391 (78.0)     | 507 (81.4)  | 1.00 (ref)          | 1213 (78.1)    | 1368 (81.7)  | 1.00 (ref)          |
| AA                | 110 (22.0)     | 116 (18.6)  | 1.32 (0.98–1.77)    | 341 (21.9)     | 307 (18.3)    | 1.27 (1.07–1.51)    |

*The observed genotype frequencies among the controls were all in agreement with the Hardy-Weinberg equilibrium in both sets (P>0.05 for all).

The merged set comprised the discovery set and the validate set.

**Statistical analysis**

The Hardy-Weinberg equilibrium (HWE) was tested by a goodness-of-fit chi-square test to compare the expected genotype frequencies with observed genotype frequencies in controls. The chi-square test was used to assess the differences in the distribution of the genotypes as well as alleles of each SNP between cases and controls. An unconditional logistic regression model with adjustment for age, sex, smoking status, drinking status and family history of cancer was used to estimate the association between SNPs and cancer risk. The best genetic model of each SNP was chose based on the smallest Akaike’s information criterion [37]. The possible interaction between SNPs and surrounding factors on another SNP rs1255722A ->G of PPP2R5E, which has a significant association with lung cancer risk. The mRNA level of PPP2R5E was detected in thirty-two lung tumor tissues [32]. Total RNA was extracted using the Trizol Reagent (Invitrogen) and reverse transcribed to complementary DNA using oligo primer and Superscript II (Invitrogen). The mRNA levels of PPP2R5E and an internal reference gene β-actin were measured on the ABI Prism 7500 sequence detection System (Applied Biosystems) using the SYBR- Green method. The primers for PPP2R5E were: 5’- TCA GCA CCA ACT CCT CCA 3’ (forward) and 5’- GCC TTG AGA CCT AAA CTG TGA G 3’ (reverse) and for β-actin were: 5’- GGC GCC ACC ACC ATG TAC CCT 3’ and 5’- AGG GCC CGG ACT CGT CAT ACT 3’. All analyses were performed in a blinded fashion with the laboratory persons unaware of genotyping data and each assay was done in triplicate.
Table 3. Stratification analysis of the association between number of risk genotypes and lung cancer risk by selected variables.

| Variables                  | Cases                      | Controls                  | Adjusted OR (95% CI) | \( P_{\text{trend}} \) | \( P_{\text{inter}} \) |
|----------------------------|----------------------------|---------------------------|----------------------|-------------------------|-------------------------|
|                            | 0 n (%)                    | 1 n (%)                   | 2 n (%)               |                         |                         |
|                            | 0 n (%)                    | 1 n (%)                   | 2 n (%)               |                         |                         |
| Totally                    | 683 (44.3)                 | 702 (45.5)                | 157 (10.2)            | 1.00 (ref.)             | 1.59 (1.23–2.06)        |
| Age (years)                |                            |                           |                       |                         |                         |
| \( \leq 60 \)              | 360 (45.1)                 | 357 (44.7)                | 82 (10.3)             | 1.00 (ref.)             | 1.52 (1.07–2.17)        |
| \( >60 \)                  | 323 (43.5)                 | 345 (46.4)                | 75 (10.1)             | 1.00 (ref.)             | 1.66 (1.14–2.42)        |
| Sex                        |                            |                           |                       |                         |                         |
| Male                       | 489 (45.4)                 | 482 (44.7)                | 107 (9.9)             | 1.00 (ref.)             | 1.70 (1.24–2.33)        |
| Female                     | 194 (41.8)                 | 220 (47.4)                | 50 (10.8)             | 1.00 (ref.)             | 1.40 (0.89–2.20)        |
| Family history of cancer   |                            |                           |                       |                         |                         |
| Yes                        | 52 (40.3)                  | 64 (49.6)                 | 13 (10.1)             | 1.00 (ref.)             | 1.53 (1.17–2.00)        |
| No                         | 631 (44.7)                 | 638 (45.2)                | 144 (10.2)            | 1.00 (ref.)             | 1.56 (1.20–2.02)        |
| Family history of lung cancer |                            |                           |                       |                         |                         |
| Yes                        | 20 (38.5)                  | 26 (50.0)                 | 6 (11.5)              | 1.00 (ref.)             | 1.16 (0.71–2.23)        |
| No                         | 663 (44.5)                 | 676 (45.4)                | 151 (10.1)            | 1.00 (ref.)             | 1.56 (1.20–2.02)        |
| Smoking status             |                            |                           |                       |                         |                         |
| Yes                        | 372 (45.9)                 | 355 (43.8)                | 84 (10.4)             | 1.00 (ref.)             | 1.18 (1.62–2.35)        |
| No                         | 311 (42.5)                 | 347 (47.5)                | 73 (10.0)             | 1.00 (ref.)             | 1.44 (1.00–2.07)        |
| Pack years smoked          |                            |                           |                       |                         |                         |
| 0                          | 311 (42.5)                 | 347 (47.5)                | 73 (10.0)             | 1.00 (ref.)             | 1.44 (1.00–2.07)        |
| <20                        | 96 (48.2)                  | 86 (43.2)                 | 17 (8.5)              | 1.00 (ref.)             | 1.62 (0.79–3.34)        |
| \( \geq 20 \)              | 276 (45.1)                 | 269 (44.0)                | 67 (10.9)             | 1.00 (ref.)             | 1.69 (1.09–2.64)        |
| Drinking status            |                            |                           |                       |                         |                         |
| Yes                        | 124 (42.8)                 | 134 (46.2)                | 32 (11.0)             | 1.00 (ref.)             | 1.42 (1.06–1.77)        |
| No                         | 559 (44.6)                 | 568 (45.4)                | 125 (10.0)            | 1.00 (ref.)             | 1.42 (1.07–1.88)        |
| Histological types         |                            |                           |                       |                         |                         |
| Adenocarcinoma             | 260 (42.7)                 | 290 (47.6)                | 59 (9.7)              | 1.00 (ref.)             | 1.54 (1.09–2.16)        |
| Squamous cell carcinoma    | 250 (48.0)                 | 217 (41.7)                | 54 (10.4)             | 1.00 (ref.)             | 1.49 (1.05–2.12)        |
| Large cell carcinoma       | 27 (41.5)                  | 32 (49.2)                 | 6 (9.2)               | 1.00 (ref.)             | 1.61 (0.65–4.00)        |
| Small cell lung cancer     | 83 (43.7)                  | 86 (45.3)                 | 21 (11.1)             | 1.00 (ref.)             | 1.78 (1.06–2.99)        |
| Other carcinomas           | 56 (39.2)                  | 70 (49.0)                 | 17 (11.9)             | 1.00 (ref.)             | 2.12 (1.19–3.76)        |
| Stages                     |                            |                           |                       |                         |                         |
| I                          | 81 (40.9)                  | 100 (50.5)                | 17 (8.6)              | 1.00 (ref.)             | 1.47 (0.84–2.56)        |
| II                         | 68 (46.9)                  | 65 (44.8)                 | 12 (8.3)              | 1.00 (ref.)             | 1.23 (0.65–2.35)        |
lung cancer risk was assessed by a multiplicative interaction model as when OR 11 > OR 10 × OR 01, in which OR 11 = the OR when both factors were present, OR 01 = the OR when only factor 1 was present, OR 10 = the OR when only factor 2 was present [38,39]. The Breslow-Day test was used to test the homogeneity between stratum-ORs. Moreover, the statistical power was calculated by using the PS Software [40]. The One-way ANOVA test and student’s t test were used to evaluate the differences in PPP2R5E expression in tumor tissues among different genotypes. All tests were two-sided by using the SAS software (version 9.3; SAS Institute, Cary, NC). P < 0.05 was considered statistically significant.

### Results

**Distribution of PP2A subunit genes genotypes and their associations with risk of lung cancer**

The genotype frequencies of above SNPs among controls were all in agreement with the Hardy-Weinberg equilibrium (P > 0.05 for all). As shown in Table 1, the logistical regression analysis showed that the -G and GG genotypes of rs11453459-G conferred a 1.29-fold and 1.51-fold increased risks of lung cancer compared to the common – genotype (-G vs. –: odds ratio [OR] = 1.29, 95% Confidence interval [CI] = 1.11–1.58, P = 0.002; while the rs1255722G >A best fitted the recessive genetic model, the rs1255722AA variant had a 27% increased lung cancer risk (OR = 1.27, 95% CI = 1.02–1.57, P = 0.031) compared to G genotypes (AG + GG). However, for the other seven SNPs, no significant association between them and lung cancer risk (P > 0.05 for all). Moreover, the rs11453459G variants were still significantly associated with increased cancer risk after multiple tests (P < 0.05 for all). We combined the two populations to increase the study power because the homogeneity test showed that the above associations in two sets were homogeneous (P = 0.974 for rs11453459-G; P = 0.559 for rs1255722G-A). The carriers of rs11453459G genotypes had a 1.31-fold increased lung cancer risk in dominant model (adjusted OR = 1.31; 95% CI = 1.13–1.51; P = 0.001), and the carriers of rs1255722AA genotype had a 1.27-fold increased risk of lung cancer in recessive model (OR = 1.27; 95% CI = 1.07–1.51; P = 0.007;
with $G$ genotypes (ANOVA test: $P_{\text{Bonferroni}} = 0.014$). In addition, the distribution of demographic characteristics and risk factors of the discovery set and validation set were presented in Table S2.

Combined genotypes and lung cancer risk

As shown in Table 3, we combined the risk genotypes of the two SNPs based on the number of risk genotypes (i.e., rs11453459G and rs1255722AA genotypes). We defined that the carriers with rs11453459– and rs1255722G genotypes have zero risk genotype; the carriers with rs11453459– and rs1255722AA, or rs11453459G and rs1255722G genotypes have one risk genotype; and the carriers with rs11453459G and rs1255722AA genotypes have two risk genotypes. We found that compared with the zero risk genotypes carriers, the one and two number of risk genotypes were associated with increased risks of lung cancer in a dose-dependent manner (OR = 1.32, 95% CI = 1.14–1.53 for one, OR = 1.59, 95% CI = 1.23–2.06 for two risk genotypes; $P_{\text{Arend}} = 5.63 \times 10^{-6}$).

Stratification analysis of the number of risk genotypes and lung cancer risk

We performed stratification analysis to evaluate the effect of surrounding factors on associations between increased number of risk genotypes and lung cancer risk. As shown in Table 3, the associations were significant in all subgroups except for in individuals with a family history of lung cancer, smokers who smoked less than 20 pack-years, subjects whose histological types is large cell carcinoma and in stage II, which may be due to the limitation of small sample sizes in these subgroups. Furthermore, we observed a positively significant interaction between number of $PPP2R1A$ and $PPP2R5E$ risk genotypes and drinking status on increasing lung cancer risk ($P = 0.034$, Table S3).

Association between the rs1255722G $>$ A genotypes and mRNA levels of $PPP2R5E$ gene

As shown in Figure 1, the mRNA levels of $PPP2R5E$ in tissues with rs1255722AA genotype were significantly lower than those with $G$ genotypes (ANOVA test: $P = 0.003$). The dichotomized analysis showed that the AA genotype was significantly associated with a decreased mRNA level of $PPP2R5E$ compared to $G$ genotypes (Student’s $t$ test: $P = 0.032$).

Bioinformatics Analysis

We further performed bioinformatics analysis to predict the biological effect of rs1255722G $>$ A on affecting the binding ability of potent transcriptional factors by using TFSEARCH (http://www.cbrc.jp/research/db/TFSEARCH.html). The software showed that the G to A transversion may result in a loss binding of a transcription factor c-Ets as the bioinformatics analysis shown. Interestingly, it is reported that c-Ets acts as transcription enhancers promoting PP2A expression in human [44]. Therefore, it is biologically conceivable that the two SNPs were associated with increased risk and their combination cause a much higher risk of lung cancer, because they may cause dysfunctional PP2A.

Moreover, we observed a positively significant interaction between the number of risk genotypes and drinking on increasing lung cancer risk. It is well known that long time alcohol consumption is a potent cancer risk factor [45], and ethanol drinking is a stimulus of PP2A activity [46], the SNP-induced low $PPP2A$ expression may cause more adverse effect in response to ethanol stimulation and thus interacted with drinking on lung carcinogenesis.

Genetic variants in $PPP2R1A$ or $PPP2R5E$ had been reported to be associated with risk of human cancers. Several SNPs in $PPP2R1A$ were reported to associated with various cancer risk including breast cancer [22] and uterine serous carcinoma [41]. Similarly, $PPP2R5E$ SNPs are susceptible loci for risk of breast cancer [47], lymphocytic leukemia [48], and soft tissue sarcoma [49]. However, these SNPs are all located in introns. Our study was unique and revealed two functional SNPs in $PPP2R1A$ and $PPP2R5E$ were associated with increased risk of lung cancer. Anyway, all these implicated the SNPs in $PPP2R1A$ and $PPP2R5E$ may be valuable biomarkers to predict risk of cancer.

Because this study is a hospital-based case-control study restricted on Chinese Han populations, some limitations are unavoidable (e.g., selection bias). However, the genotype frequencies among controls fitted the Hardy-Weinberg disequilibrium law and suggested the randomness of subject selection. And the study powers were acceptable, we have achieved a 95.5% study power (two-sided test, $\alpha = 0.05$) to detect an OR of 1.31 for the rs11453459G genotypes (37.1% in the controls), and 88.3% study power to detect an OR of 1.27 for the rs1255722AA genotype (which occurred at a frequency of 18.3% in the controls). Meanwhile, the associations were also functional possible. Moreover, results from the GWAS also showed that the frequency distribution of SNP rs1255722G $>$ A was significantly different between cases and controls (rs1255722: $P = 0.014$) [23], but the SNP rs11453459-$G$ was not included in the Affymetrix® Genome-Wide Human SNP Array 6.0. Thus, it appears that our finding that the associations between PP2A subunit gene variants and increased risk of lung cancer is unlikely to have been achieved by chance.

In conclusion, our data suggested that the two functional SNPs (rs11453459-$G$ of $PPP2R1A$ and rs1255722AA $>$ G of $PPP2R5E$) are associated with risk of lung cancer in Chinese. The
identification and description of these two SNPs may lead to their use as genetic biomarker like personalized prevention and therapeutic strategy. Validations with larger population-based studies in different ethnic groups are warranted.

Supporting Information

Table S1  Primary information on the TAQMAN assay of nine SNPs in PP2A subunit genes.

Table S2  Frequency distributions of selected variables in lung cancer patients and cancer-free controls.

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Table S3  The interaction between the number of risk genotypes and drinking on increasing lung cancer risk by a multiple interaction analysis interaction.

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Author Contributions

Conceived and designed the experiments: JL YZ. Performed the experiments: RY LZ HW XY. Analyzed the data: LY. Contributed reagents/materials/analysis tools: JD WF. Wrote the paper: RY. Revision of the paper: LY YZ JL.
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