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Research Article

Association of Single-Nucleotide Polymorphism *REX1* rs6815391, *OCT4* rs13409 or rs3130932, and *CTBP2* rs3740535 with Primary Lung Cancer Susceptibility: A Case-Control Study in a Chinese Population

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The purpose of the current study is to explore the contribution of single-nucleotide polymorphisms (SNPs) of *REX1* rs6815391, *OCT4* rs13409 or rs3130932, and *CTBP2* rs3740535 to the risk of lung cancer. A questionnaire survey was used to obtain basic information of the included subjects. A case control study was performed in 1121 patients and 1121 controls. All subjects were subjected to blood sampling for genomic DNA extraction and genotyping of the cancer stem cell-associated gene SNPs, including *REX1* rs6815391, *OCT4* rs13409 or rs3130932, and *CTBP2* rs3740535 by real-time PCR. The association with the risk of primary lung cancer and interaction with environmental factors were assessed using unconditional logistic regression for the odds ratios and corresponding 95% confidence intervals. The genotype frequency distribution of *OCT4* rs13409 loci was statistically significant, but there was no significant difference in the rest of the loci between lung cancer patients and healthy controls. The *OCT4* gene was also related with lung cancer susceptibility in the genetic model after adjusting for lung cancer-related factors. Despite the presence of the dominant or recessive model, the four loci polymorphisms were associated with pollution near the place of residence, house type, worse ventilation situation, smoking, passive smoking, cooking oil fumes (COF), and family history of cancer, which increased the risk of lung cancer. Nonmarried status, $18.5 \leq$ BMI, COF, smoking, passive smoking, family history of cancer, and history of lung disease were independent risk factors of lung cancer susceptibility. Additionally, college degree or above, no pollution near the place of residence, protective genotype 1 or 2, and well ventilation can reduce the occurrence of lung cancer. There is an interaction between the four loci and environmental factors, and *OCT4* rs13409 is a risk factor of primary lung cancer.

1. Introduction

Lung cancer is a common malignancy and the most frequent reason of malignancy-associated death worldwide; additionally, approximately 1.8 million new lung cancer patients were diagnosed in 2012, accounting for approximately 13% of total malignancy diagnoses [1]. In 2015, there were 733,000 new lung cancer cases and 660,000 cases of death in China [2]. Smoking is the key risk factor of pulmonary cancer [3]; nevertheless, despite a lower popularity of tobacco use in China,

lung cancer prevalence in Chinese females is higher than in females of several European countries [1]. This indicated that other risk factors, for example genetic factors, may be part of the cause in the development of lung cancer.

Lung cancer is caused by a variety of factors. Single-nucleotide polymorphisms (SNPs) play fundamental roles in tumorigenesis, cancer development, and prognosis. SNPs can modify gene product sequences, regulate gene expression, and influence gene function to change the phenotype.

The pluripotency and self-renewal characteristics of embryonic cells involved multiple levels of cells and a variety of factors, and the coding of stem cell signaling molecules in the genetic polymorphism may be involved in cancer occurrence [4–6]. Cancer stem cells (CSCs) have been recognized as the major source of cancer initiation and recurrence. Elevated *OCT4* expression has been reported in many tumor types including NSCLC, and the expression levels of *OCT4* mRNA and protein were significantly higher in tumor tissues compared with adjacent normal tissues [7]. Researchers revealed that *OCT4* is linked to chemoresistance to cisplatin in NSCLC cells, suggesting that *OCT4* inhibition may be a potential strategy for chemosensitization of NSCLC cells [8]. Clinical studies further validated the importance of the *OCT4*/*NEAT1*/*MALAT1* signaling axis in lung cancer progression [9].

OCT4, the "core transcription factor," plays important roles in self-renewal, tumorigenesis, invasiveness, and drug resistance of cancer stem cells [10]. *OCT4* is associated with many types of cancer, including lung cancer [11], germ cell tumors [12], breast cancer [13], cervical cancer [14], prostate cancer [15], stomach cancer [16], liver cancer [17], and ovarian cancer [18]. In embryonic stem cells, *OCT4* has been identified to regulate the transcriptions of other transcription factors, chromatin modifiers, long noncoding RNAs (lncRNAs), and microRNAs [19]. The *OCT4*gene binding inhibitory complex makes stem cells lose pluripotency. For example, miR-45 as acts as a tumor inhibitor by regulating the expression of *OCT4* to reduce lung cancer initiation by tumor stem cells as well as their epithelial mesenchymal transition (epithelial-mesenchymal transition (EMT)). miR-45 also inhibited tumor growth and metastasis in lung adenocarcinoma [20]. Additionally, genes involved in the maintenance of pluripotency, such as *Fgf4*, *Utf1*, *Zfp42*/*REX1*, and *Opn*, are all downstream genes of *OCT4* [21].

REX1 regulates the growth and development of embryonic stem cells and reacts with *OCT4* [22]. *REX1* not only inhibits the transcriptional activation of *OCT4* to induce stem cell apoptosis but also independently regulates growth inhibition, apoptotic cell death, cell cycle arrest, and DNA damage [23].

The whole genome sequence analysis and functional experiments showed that the most prominent synergistic factor in the transcriptional repression complex was NuRD, and CTBP is an important ligand for the transcriptional inhibition of NuRD [24]. The combination of NuRD and *CTBP2* leads to the deacetylation of embryonic stem cells and the disappearance of the pluripotency of stem cells. A new study showed that *CtBP2* knockdown enhanced NSCLC cell sensitivity to CDDP through inhibition of the Wnt/β-catenin pathway, which suggests that *CtBP2* depletion can provide a new target for NSCLC treatment [25]. *REX1* (upstream of *OCT4*), *CTBP2* (downstream of *OCT4*), and *OCT4* synthetically can inhibit stem cell proliferation and regulate cancer stem cell apoptosis. We intended to explore the association between SNPS of three genes in this pathway and lung cancer susceptibility. The SNP rs13409 of the *OCT4* gene showed significant associations with multiple myeloma risks from a previously published genome-wide association study (GWAS); the *OCT4* rs3130932 was associated with gastric cancer and breast cancer. However, there are few studies on *REX1* rs6815391 and *CTBP2* rs3740535. Thus, we selected *REX1* rs6815391, *OCT4* rs13409, rs3130932, and *CTBP2* rs3740535.

2. Materials and Method

2.1. Subjects. 1121 newly diagnosed (enrolled in the study at the time of cancer diagnosis) primary lung cancer patients were recruited from three hospitals of the First Clinical Medical College of Fujian Medical University, Fuzhou General Hospital, and the Affiliated Union Hospital of Fujian Medical University, from July 2006 to February 2013. The control group consisted of 1121 age-matched (±2 years) cancer-free individuals recruited from medical examination centers or hospital nononcology departments during the same period. All subjects were Chinese Han who were living in Fujian for >10 years and were able to answer questions clearly. The response rate for subjects was 92.68%. This study was approved by the Institutional Review Board of Fujian Medical University (Fuzhou, China), and all participants signed the informed consent forms.

2.2. Questionnaire. A unified standard questionnaire according to the principle of informed consent was used. The investigators accepted a unified training for the face-to-face interview survey. The survey includes the general situation (age, gender, ethnicity, education, marital status, height, weight, etc.), living environment, diet history, alcohol drinking history, smoking history, tea drinking history, lung disease history, family history of cancer, and history of physical activity.

The education degree was divided into three levels: primary school or below, junior and senior high school, and college degree or above. The marital status included three grades: married, others (divorced and widowed), and single. We calculated the body mass index (BMI) as body weight (kg)/height^2 (m^2). House types included bungalow, building, and others. There were three different ventilation situations, well, general, or worse, which was judged according to the ventilation of the bedroom. To evaluate cooking oil fume (COF) exposure, the fumes in the kitchen during cooking were classified into no fumes, little fumes, some fumes, or much fumes. Redecoration within 10 years, smoking, passive smoking, tea drinking, history of lung disease, and family history of cancer were provided with a binary response ("no" or "yes"). The kitchen ventilator was a machine that sucked cooking oil fumes out of the kitchens. Redecoration within 10 years indicated that the interior had been redecorated or

Table 1: Demographic characteristics of the included patients and healthy control.

Variable	Case group (%)	Control group (%)	OR (95% CI)
Age			
≤52	295 (26.3)	289 (25.8)	1.000
53-59	285 (25.4)	273 (24.4)	1.012 (0.802-1.278)
60-66	272 (24.3)	274 (24.4)	0.973 (0.770-1.228)
≥67	269 (24.0)	285 (25.4)	0.925 (0.733-1.167)
Gender			
Male	797 (71.1)	797 (71.1)	1.000
Female	324 (28.9)	324 (28.9)	1.000 (0.833-1.200)
Degree of education			
Primary school or below	564 (50.4)	418 (37.3)	1.000
Junior and senior high school	443 (39.6)	553 (49.3)	*0.594 (0.497-0.709)*
College degree or above	114 (10.2)	150 (13.4)	*0.563 (0.428-0.741)*
Marital status			
Married	1054 (94.0)	1039 (92.7)	1.000
Others	64 (5.7)	66 (5.9)	0.956 (0.671-1.362)
Single	3 (0.3)	16 (1.4)	*0.185 (0.054-0.636)*
BMI ($kg/m^{2)}$			
<18.5	124 (11.1)	51 (4.5)	1.000
18.5-23.9	694 (61.9)	613 (54.7)	*0.466 (0.330-0.657)*
≥24	303 (27.0)	457 (40.8)	*0.273 (0.191-0.390)*
Pollution near the place of residence			
Not	900 (80.3)	1026 (91.5)	1.000
Exist	221 (19.7)	95 (8.5)	*2.652 (2.052-3.428)*
House type			
Bungalow	377 (33.6)	182 (16.2)	1.000
Building	734 (65.5)	931 (83.1)	*0.381 (0.311-0.466)*
Others	10 (0.9)	8 (0.7)	0.603 (0.234-1.555)
Ventilation situation			
Well	859 (76.6)	990 (88.3)	1.000
General	223 (19.9)	115 (10.3)	*2.235 (1.753-2.849)*
Worse	39 (3.5)	16 (1.4)	*2.809 (1.559-5.063)*
Cooking oil fume (COF)			
No	190 (16.9)	350 (31.2)	1.000
Little	613 (54.7)	544 (48.5)	*2.076 (1.681-2.563)*
Some	269 (24.0)	205 (18.3)	*2.417 (1.876-3.114)*
Much	49 (4.4)	22 (2.0)	*4.103 (2.407-6.992)*
Kitchen ventilator			
No	480 (42.8)	337 (30.1)	1.000
Yes	641 (57.2)	784 (69.9)	*0.574 (0.482-0.683)*
Decoration within 10 years			
No	674 (60.1)	692 (61.7)	1.000
Yes	447 (39.9)	429 (38.3)	1.070 (0.903-1.268)
Smoking			
No	425 (37.9)	659 (58.8)	1.000
Yes	696 (62.1)	462 (41.2)	*2.336 (1.972-2.767)*
Passive smoking			
No	335 (29.9)	621 (55.4)	1.000
Yes	786 (70.1)	500 (44.6)	*2.914 (2.449-3.467)*

Table 1: Continued.

Variable	Case group (%)	Control group (%)	OR (95% CI)
Drink alcohol			
No	733 (65.4)	805 (71.8)	1.000
Yes	388 (34.6)	316 (28.2)	*1.348 (1.127-1.613)*
Drink tea			
No	566 (50.5)	537 (47.9)	1.000
Yes	555 (49.5)	584 (52.1)	0.902 (0.764-1.064)
History of lung disease			
No	983 (87.7)	1025 (91.4)	1.000
Yes	138 (12.3)	96 (8.6)	*1.499 (1.139-1.973)*
Family history of cancer			
No	900 (80.3)	950 (84.7)	1.000
Yes	221 (19.7)	171 (15.3)	*1.364 (1.095-1.699)*

BMI = weight (kg)/height^2 (m^2).

painted within the last 10 years. Smoking status was defined as individuals who had smoked at least 100 cigarettes during their lifetime. Passive smoking was defined as exposure to other environmental sources of tobacco smoke at home and/or at work for more than 15 minutes per day. Drinking alcohol was defined as drinking at least once per week for more than half a year. Tea drinkers were defined as those who consumed at least 1 cup of tea per day, for at least 6 consecutive months. History of lung disease referred to a history of chronic bronchitis, emphysema, tuberculosis, and other chronic respiratory diseases. Family history of cancer was any type of cancer in any immediate family member.

2.3. Study Protocol

2.3.1. Sample Collection and DNA Isolation. Peripheral blood samples were obtained from both patients and control subjects included in this study and stored in EDTA tubes. Protease K digestion and phenol-chloroform extraction were used to extract the genomic DNA from blood samples. The purified genomic DNA was stored at -20°C until being used for SNP genotyping.

2.3.2. Genotyping. Genotyping [26] was performed at the UCLA Genotype and Sequencing Core, with a customized Fluidigm Dynamic 96.96 Array™ Assay (Fluidigm, South San Francisco, CA). The assays were based on allele-specific PCR SNP detection chemistry with Dynamic Array™ integrated fluidic circuits (IFCs). The SNP Type Assay employed tagged, allele-specific PCR primers and a common reverse primer. A universal probe set was used in every reaction, producing uniform fluorescence. Fluidigm provided locus-specific primer sequences that allowed one to confirm target locations.

The genomic DNA was used for SNP genotyping with the Sequenom platform in accordance with the manufacturer's iPLEX Application Guide (Sequenom Inc., San Diego, CA). The samples were scanned using a matrix-assisted laser desorption ionization-time of flight mass spectrometry system and genotyped with a MassARRAY Typer 3.4 (Sequenom Inc., San Diego, CA). For quality control, approximately 10% of randomly selected samples were rerun. The concordance rate was 99.5%, and the genotyping call rates reached >90%.

2.4. Statistical Analysis. IBM SPSS 21.0 software (Armonk, NY, USA) was used, and the statistical significance was set to 0.05. Demographic features between lung cancer patients and healthy controls were compared by a 2-sided chi-squared test to identify the potential differences. An online calculator with α of 0.05 was used to evaluate the Hardy-Weinberg equilibrium for each SNP. The odds ratio (OR) was calculated with an unconditional logistic regression model, and the risk of lung cancer developing for polymorphisms among study subjects was estimated by 95% confidence interval (CI); the possible confounding factors, for example age and education, were controlled to analyze the adjusted OR. The relative excess risk because of interaction, the attributable proportion because of interaction, the synergy index, and its 95% CI were used to evaluate the association between the four SNPs and lung cancer.

2.5. Ethics Statement. Our study was approved by the Ethical Committee of Fujian Medical University (Fuzhou, China) ([2014] Fu Yi Ethics Review (No. 98)), and all participants signed the informed consent forms.

3. Results

3.1. Demographic Characteristics and Environmental Factors. The demographic characteristics of 1121 patients and 1121 controls are listed in Table 1. There were no significant differences ($P > 0.05$) between the patient group and control group including age, gender, redecoration within 10 years, and drinking tea. However, there was a significant difference in the distribution of the educational history, marital status, BMI, pollution near the place of residence, house type, ventilation situation, COF, kitchen ventilator, smoking, passive smoking, drinking alcohol, history of lung

Table 2: Association of rs13409 SNP with susceptibility to lung cancer.

	Genotyping	Case (%) $N = 1022$	Control (%) $N = 1053$	OR (95% CI)	a(OR (95% CI)#
Codominant	CC	512 (50.1)	466 (44.3)	1.000	1.000
	CT	389 (38.1)	478 (45.4)	0.741 (0.617-0.890)	*0.731 (0.595-0.899)*
	TT	121 (11.8)	109 (10.3)	1.010 (0.758-1.347)	0.908 (0.657-1.257)
Dominant	CC	512 (50.1)	466 (44.3)	1.000	1.000
	CT+TT	510 (49.9)	587 (55.7)	0.791 (0.665-0.940)	*0.765 (0.629-0.930)*
Recessive	CC+CT	901 (88.2)	944 (89.7)	1.000	1.000
	TT	121 (11.8)	109 (10.3)	1.163 (0.884-1.530)	1.054 (0.774-1.436)
Additive				0.908 (0.799-1.032)	0.873 (0.755-1.009)

#By the degree of education, marital status, BMI, pollution near the place of residence, house type, ventilation situation, COF, kitchen ventilator, smoking, passive smoking, drink alcohol, history of lung disease, and family history of cancer adjusted. OR and its interval shown in italic font to represent $P < 0.05$.

Table 3: Association of another three SNPs with susceptibility to lung cancer.

	Classification	Case (%) $N = 1020$	Control (%) $N = 1033$	OR (95% CI)	aOR (95% CI)#
rs6815391 $P_{HWE} = 0.099$					
Codominant	TT	477 (46.8)	472 (45.7)	1.000	1.000
	CT	438 (42.9)	435 (42.1)	0.996 (0.829-1.197)	0.901 (0.732-1.109)
	CC	105 (10.3)	126 (12.2)	0.825 (0.618-1.100)	0.925 (0.670-1.279)
Dominant	TT	477 (46.8)	472 (45.7)	1.000	1.000
	CT+CC	543 (53.2)	561 (54.3)	0.958 (0.805-1.139)	0.906 (0.745-1.102)
Recessive	TT+CT	915 (89.7)	907 (87.8)	1.000	1.000
	CC	105 (10.3)	126 (12.2)	0.826 (0.628-1.087)	0.973 (0.715-1.323)
Additive				0.936 (0.823-1.065)	0.942 (0.814-1.089)
rs3740535 $P_{HWE} = 0.890$					
Codominant	GG	602 (57.4)	614 (56.9)	1.000	1.000
	AG	373 (35.6)	401 (37.1)	0.949 (0.792-1.136)	0.916 (0.747-1.124)
	AA	73 (7.0)	64 (6.0)	1.163 (0.817-1.657)	1.067 (0.714-1.594)
Dominant	GG	602 (57.4)	614 (56.9)	1.000	1.000
	AG+AA	446 (42.6)	465 (43.1)	0.978 (0.824-1.162)	0.937 (0.772-1.139)
Recessive	AG+GG	975 (93.0)	1015 (94.0)	1.000	1.000
	AA	73 (7.0)	64 (6.0)	1.187 (0.839-1.680)	1.103 (0.744-1.636)
Additive				1.013 (0.882-1.163)	0.974 (0.833-1.139)
rs3130932 $P_{HWE} = 0.986$					
Codominant	TT	453 (43.4)	453 (41.8)	1.000	1.000
	GT	460 (44.0)	494 (45.7)	0.931 (0.776-1.117)	0.890 (0.725-1.093)
	GG	132 (12.6)	135 (12.5)	0.978 (0.744-1.285)	1.031 (0.757-1.404)
Dominant	TT	453 (43.4)	453 (41.8)	1.000	1.000
	GT+GG	592 (56.6)	629 (58.2)	0.941 (0.793-1.118)	0.919 (0.757-1.116)
Recessive	GT+TT	913 (87.4)	947 (87.5)	1.000	1.000
	GG	132 (12.6)	135 (12.5)	1.014 (0.785-1.311)	1.095 (0.819-1.463)
Additive				0.972 (0.857-1.101)	0.977 (0.848-1.125)

#By the degree of education, marital status, BMI, pollution near the place of residence, house type, ventilation situation, COF, kitchen ventilator, smoking, passive smoking, drink alcohol, history of lung disease, and family history of cancer adjusted.

disease, and family history of cancer between cases and controls ($P < 0.05$) (Table 1).

3.2. The Relationship between the Four SNPs and Susceptibility to Lung Cancer. The results of unconditional logistic regression analysis showed that there was no association between *REX1* rs6815391, *OCT4* rs3130932, or *CTBP2* rs3740535 polymorphisms with susceptibility to lung cancer after adjusting for lung cancer-related factors, whether in codominant or dominant, recessive, additive, or genetic

Table 4: Association of the four SNPs of different pathological types with susceptibility to lung cancer.

Classification	Lung adenocarcinoma Case/control	*aOR* (95% CI)[#]	Lung squamous cell carcinoma Case/control	*aOR* (95% CI)[#]	Total Case/control	*aOR* (95% CI)[#]
rs13409 Codominant						
CC	252/466	1.000	147/466	1.000	490/466	1.000
CT	177/478	*0.689 (0.536-0.885)*	109/478	0.756 (0.543-1.053)	369/478	*0.734 (0.610-0.884)*
TT	58/109	0.987 (0.672-1.450)	30/109	0.754 (0.444-1.282)	113/109	0.986 (0.736-1.320)
rs13409 Dominant						
CC	352/466	1.000	147/466	1.000	490/466	1.000
CT+TT	235/587	*0.745 (0.589-0.941)*	139/587	0.756 (0.553-1.033)	482/587	*0.781 (0.656-0.930)*
rs13409 Recessive						
CC+CT	429/944	1.000	256/944	1.000	859/944	1.000
TT	58/109	1.171 (0.811-1.692)	30/109	0.861 (0.518-1.430)	859/109	1.039 (0.862-1.506)
rs13409 Additive		0.879 (0.737-1.048)		0.827 (0.653-1.047)		0.897 (0.788-1.022)
rs6815391 Codominant						
TT	230/472	1.000	136/472	1.000	452/472	1.000
CT	205/435	0.905 (0.705-1.161)	125/435	1.028 (0.740-1.428)	418/435	1.003 (0.833-1.209)
CC	49/126	0.836 (0.562-1.241)	26/126	0.830 (0.482-1.429)	101/126	0.837 (0.625-1.121)
rs6815391 Dominant						
TT	230/472	1.000	136/472	1.000	452/472	1.000
CT+CC	254/561	0.890 (0.703-1.126)	151/561	0.986 (0.722-1.348)	519/561	0.966 (0.810-1.152)
rs6815391 Recessive						
TT+CT	435/907	1.000	261/907	1.000	870/907	1.000
CC	49/126	0.876 (0.600-1.278)	26/126	0.819 (0.488-1.377)	101/126	0.836 (0.633-1.103)
rs6815391 Additive		0.911 (0.764-1.086)		0.952 (0.752-1.204)		0.943 (0.828-1.074)
rs3740535 Codominant						
GG	295/614	1.000	159/614	1.000	571/614	1.000
AG	169/401	0.875 (0.683-1.123)	114/401	1.034 (0.748-1.430)	354/401	0.949 (0.791-1.140)
AA	35/64	0.968 (0.598-1.567)	19/64	1.243 (0.650-2.375)	72/64	1.210 (0.848-1.726)
rs3740535 Dominant						
GG	295/614	1.000	159/614	1.000	571/614	1.000
GA+AA	204/465	0.889 (0.702-1.126)	133/465	1.061 (0.778-1.447)	426/465	0.985 (0.828-1.172)
rs3740535 Recessive						
GA+GG	464/1015	1.000	273/1015	1.000	925/1015	1.000
AA	35/64	1.018 (0.634-1.632)	19/64	1.226 (0.650-2.314)	72/64	1.234 (0.871-1.749)
rs3740535 Additive		0.930 (0.769-1.124)		1.073 (0.834-1.381)		1.024 (0.891-1.178)
rs3130932 Codominant						
TT	228/453	1.000	119/453	1.000	432/453	1.000
GT	213/494	0.786 (0.613-1.008)	124/494	1.030 (0.737-1.440)	438/494	0.930 (0.773-1.118)
GG	57/135	0.893 (0.611-1.307)	46/135	1.593 (0.999-2.541)	125/135	0.971 (0.736-1.280)

Table 4: Continued.

Classification	Lung adenocarcinoma Case/control	*aOR* (95% CI)[#]	Lung squamous cell carcinoma Case/control	*aOR* (95% CI)[#]	Total Case/control	*aOR* (95% CI)[#]
rs3130932 Dominant						
TT	228/453	1.000	119/453	1.000	432/453	1.000
GT+GG	270/629	0.807 (0.639-1.021)	170/629	1.146 (0.838-1.567)	563/629	0.939 (0.789-1.117)
rs3130932 Recessive						
GT+TT	441/947	1.000	243/947	1.000	870/947	1.000
GG	57/135	1.009 (0.705-1.446)	46/135	*1.569 (1.016-2.425)*	125/135	1.008 (0.777-1.307)
rs3130932 Additive		0.894 (0.752-1.064)		1.201 (0.961-1.501)		0.969 (0.853-1.100)

[#]By the degree of education, marital status, BMI, pollution near the place of residence, house type, ventilation situation, COF, kitchen ventilator, smoking, passive smoking, drink alcohol, history of lung disease, and family history of cancer adjusted. OR and its interval shown in italic font to represent the $P < 0.05$.

models. Only *OCT4* rs13409 was associated with lung cancer occurrence. In the co-dominant model, the lung cancer risk of the *OCT4* rs13409 CT genotype carriers was 0.731-fold that of the CC genotype carriers (95% CI: 0.595-0.899, $P < 0.05$); in the dominant model, the risk of lung cancer in the CT+TT genotype carriers was 0.765-fold that of the CC carriers (95% CI: 0.629-0.930, $P < 0.05$) (Tables 2 and 3).

3.3. Pathological Stratification Analysis. There was no significant difference between *CTBP2* rs3740535 and *REX1* rs6815391 polymorphism with lung cancer occurrence regardless of adenocarcinoma, squamous, or any type of lung cancer.

For the adenocarcinoma patients with *OCT4* rs13409, the risk of lung cancer in CT genotype carriers was 0.689-fold (95% CI: 0.536-0.885, $P < 0.05$) that of the CC carriers according to the co-dominant model; the lung cancer risk of CT+TT carriers was 0.745-fold that of the CC carriers (95% CI: 0.589-0.941, $P < 0.05$) by the dominant model. For all lung cancer types with *OCT4* rs13409, a risk of lung cancer in the CT genotype carriers was 0.734-fold (95% CI: 0.610-0.884, $P < 0.05$) that of the CC carriers according to the co-dominant model; the lung cancer risk of CT+TT carriers was 0.781-fold that of the CC carriers (95% CI: 0.656-0.930, $P < 0.05$).

Regarding squamous cell carcinoma, the risk of lung cancer in *OCT4* rs3130932 GG carriers was 1.569-fold (95% CI: 1.016-2.425, $P < 0.05$) that of the GT+TT carriers according to the recessive models (Table 4).

3.4. Combination and Interaction Analysis. We analyzed the interactions between the four genotypes and the environment factors including pollution near the place of residence, house type, COF, ventilation situation, kitchen ventilator, smoking, passive smoking, drink alcohol, history of lung disease, and family history of cancer (Tables 5 and 6).

The interaction analysis for both the dominant or recessive models showed that there was no additive interaction between the *REX1* rs6815391, *OCT4* rs13409 or rs3130932, or *CTBP2* rs3740535 polymorphisms with smoking (Table 7).

3.5. Multivariate Analysis. As can be observed in Tables 2 and 3, *REX1* rs6815391 CT+CC, *OCT4* rs13409 CT+TT, and rs3130932 GT+TT were three protective genotypes, and the combination could be divided into three classes. In a collinear diagnosis, the results of multivariate analysis, marital status, BMI, COF, smoking, passive smoking, family history of cancer, history of lung disease, and lung cancer susceptibility were all independent risk factors. College or above, well ventilation, one or two protective genotypes, and no pollution near the place of residence reduced the occurrence of lung cancer (Table 8).

4. Discussion

In our current study, the relationship between each of the four SNPs and the risk of lung cancer among 1121 patients and 1121 controls were estimated. The unconditional logistic regression analysis results showed no association between *REX1* rs6815391, *OCT4* rs3130932, or *CTBP2* rs3740535 with lung cancer susceptibility, whereas *OCT4* rs13409 was associated with lung cancer susceptibility. In the co-dominant model, the lung cancer risk of the *OCT4* rs13409 CT genotype carriers was 0.731-fold that of the CC genotype carriers (95% CI: 0.595-0.899); in the dominant model, the risk of lung cancer in the CT+TT genotype carriers was 0.765-fold that of the CC carriers (95% CI: 0.629-0.930).

REX1, also known as *Zfp42*, belongs to the zinc finger protein C2H2 family and is one of the subgroup members of the transcription factor YY1 (Yin Yang 1) [27]. The expression of the *REX1* molecule occurs mainly in the early stages of embryonic development, and its deletion may not directly affect the differentiation direction of ES cells but may play a role in the late developmental stage [28].

The expression of *REX1* was detected in different cells, such as bone marrow, heart, human epidermal keratinocytes, prostate, and lung-derived epithelial cells but disappeared with the increase in cell passage times, suggesting that *REX1* expression is closely related to cell self-renewal [15]. The *REX1* promoter contains binding sites for multiple core transcription factors and has a two-way regulatory effect with the *OCT4* gene, which plays a role in the pluripotency of stem

Table 5: Joint and multiplication interaction between gene dominant model and environmental factors.

Genotype	Environment	Case (%)	Control (%)	OR (95% CI)	aOR (95% CI)[#]
rs13409		$N = 1022$	$N = 1053$		
rs13409 with pollution near the place of residence					
CC	No	414 (40.5)	429 (40.7)	1.000	1.000
CC	Yes	98 (9.6)	37 (3.5)	2.745 (1.837-4.101)	*2.467 (1.595-3.816)*
CT+TT	No	410 (40.1)	540 (51.3)	0.787 (0.653-0.948)	*0.760 (0.617-0.936)*
CT+TT	Yes	100 (9.8)	47 (4.5)	2.205 (1.520-3.198)	*1.980 (1.316-2.977)*
rs13409 × pollution near the place of residence		$OR^{multiply}$ (95% CI)		2.322 (1.623-3.321)	*2.119 (1.432-3.138)*
rs13409 with house type					
CC	No	174 (17.0)	80 (7.6)	1.000	1.000
CC	Yes	338 (33.1)	386 (36.7)	0.403 (0.298-0.545)	*0.504 (0.358-0.711)*
CT+TT	No	174 (17.0)	93 (8.8)	0.860 (0.597-1.240)	0.761 (0.510-1.136)
CT+TT	Yes	336 (32.9)	494 (46.9)	0.313 (0.232-0.422)	*0.387 (0.276-0.542)*
rs13409 × house type		$OR^{multiply}$ (95% CI)		0.554 (0.464-0.662)	*0.627 (0.513-0.766)*
rs13409 with ventilation situation					
CC	No	17 (1.7)	8 (0.8)	1.000	1.000
CC	Yes	495 (48.4)	458 (43.5)	0.509 (0.217-1.190)	0.654 (0.257-1.665)
CT+TT	No	19 (1.9)	7 (0.7)	1.277 (0.382-4.271)	1.305 (0.350-4.862)
CT+TT	Yes	491 (48.0)	580 (55.1)	0.398 (0.170-1.931)	0.497 (0.196-1.264)
rs13409 × ventilation situation		$OR^{multiply}$ (95% CI)		0.754 (0.635-0.896)	*0.652 (0.533-0.798)*
rs13409 with kitchen ventilator					
CC	No	215 (21.0)	138 (13.1)	1.000	1.000
CC	Yes	297 (29.1)	328 (31.1)	0.581 (0.446-0.758)	0.973 (0.712-1.330)
CT+TT	No	224 (21.9)	177 (16.8)	0.812 (0.607-1.086)	0.808 (0.583-1.120)
CT+TT	Yes	286 (28.0)	410 (38.9)	0.448 (0.345-0.582)	*0.722 (0.530-0.984)*
rs13409 × kitchen ventilator		$OR^{multiply}$ (95% CI)		0.609 (0.507-0.733)	*0.771 (0.623-0.954)*
rs13409 with COF					
CC	No	84 (8.2)	153 (14.5)	1.000	1.000
CC	Yes	428 (41.9)	313 (29.7)	2.491 (1.839-3.374)	*2.101 (1.497-2.949)*
CT+TT	No	88 (8.6)	182 (17.3)	0.881 (0.609-1.273)	0.855 (0.569-1.286)
CT+TT	Yes	422 (41.3)	405 (38.5)	1.898 (1.407-2.559)	*1.572 (1.124-2.197)*
rs13409 × COF		$OR^{multiply}$ (95% CI)		1.125 (0.944-1.342)	*0.890 (0.837-0.946)*
rs13409 with smoking					
CC	No	202 (19.8)	264 (25.1)	1.000	1.000
CC	Yes	310 (30.3)	202 (19.2)	2.006 (1.554-2.588)	*1.657 (1.231-2.230)*
CT+TT	No	189 (18.5)	361 (34.3)	0.684 (0.531-0.882)	*0.641 (0.485-0.849)*
CT+TT	Yes	321 (31.4)	226 (21.5)	1.856 (1.446-2.384)	*1.496 (1.113-2.011)*
rs13409 × smoking		$OR^{multiply}$ (95% CI)		1.676 (1375-2.042)	*1.374 (1.093-1.727)*
rs13409 with passive smoking					
CC	No	156 (15.3)	267 (25.4)	1.000	1.000
CC	Yes	356 (34.8)	199 (18.9)	3.062 (2.354-3.982)	*2.404 (1.081-3.209)*
CT+TT	No	151 (14.8)	317 (30.1)	0.815 (0.618-1.075)	0.766 (0.567-1.037)
CT+TT	Yes	359 (35.1)	270 (25.6)	2.276 (1.767-2.930)	*1.837 (1.392-2.423)*
rs13409 × passive smoking		$OR^{multiply}$ (95% CI)		1.570 (1.300-1.897)	*1.402 (1.138-1.727)*
rs13409 with drink alcohol					
CC	No	343 (33.6)	329 (31.2)	1.000	1.000
CC	Yes	169 (16.5)	137 (13.0)	1.183 (0.902-1.552)	0.800 (0.581-1.100)
CT+TT	No	328 (32.1)	421 (40.0)	0.747 (0.606-0.921)	*0.736 (0.581-0.932)*

Table 5: Continued.

Genotype	Environment	Case (%)	Control (%)	OR (95% CI)	aOR (95% CI)[#]
CT+TT	Yes	182 (17.8)	166 (15.8)	1.052 (0.812-1.363)	*0.665 (0.492-0.900)*
rs13409 × drink alcohol		$OR^{multiply}$ (95% CI)		1.158 (0.919-1.458)	0.793 (0.608-1.034)
rs13409 with history of lung disease					
CC	No	452 (44.2)	422 (40.1)	1.000	1.000
CC	Yes	60 (5.9)	44 (4.2)	1.273 (0.844-1.920)	1.087 (0.680-1.737)
CT+TT	No	442 (43.2)	542 (51.5)	0.761 (0.634-0.914)	*0.724 (0.589-0.889)*
CT+TT	Yes	68 (6.7)	45 (4.3)	1.411 (0.946-2.103)	1.364 (0.866-2.147)
rs13409 × history of lung disease		$OR^{multiply}$ (95% CI)		1.597 (1.084-2.351)	*1.596 (1.028-2.477)*
rs13409 with family history of cancer					
CC	No	403 (39.4)	395 (37.5)	1.000	1.000
CC	Yes	109 (10.7)	71 (6.7)	1.505 (1.082-2.092)	1.495 (1.032-2.167)
CT+TT	No	412 (40.3)	501 (47.6)	0.806 (0.666-0.975)	*0.769 (0.620-0.953)*
CT+TT	Yes	98 (9.6)	86 (8.2)	1.117 (0.810-1.540)	1.116 (0.777-1.603)
rs13409 × family history of cancer		*$OR^{multiply}$ (95% CI)*		1.193 (0.881-1.615)	1.218 (0.865-1.714)
rs6815391		*N* = 1020	*N* = 1033		
rs6815391 with pollution near the place of residence					
TT	No	385 (37.7)	425 (41.1)	1.000	1.000
TT	Yes	92 (9.0)	47 (4.5)	2.161 (1.481-3.152)	*1.978 (1.311-2.984)*
CT+CC	No	436 (42.7)	522 (50.5)	0.922 (0.764-1.112)	0.862 (0.699-1.064)
CT+CC	Yes	107 (10.5)	39 (3.8)	3.029 (2.047-4.481)	*2.516 (1.647-3.845)*
rs6815391 × pollution near the place of residence		$OR^{multiply}$ (95% CI)		2.987 (2.048-4.357)	*2.571 (1.710-3.865)*
rs6815391 with house type					
TT	No	140 (13.7)	73 (7.1)	1.000	1.000
TT	Yes	337 (33.0)	399 (38.6)	0.440 (0.320-0.605)	*0.638 (0.444-0.915)*
CT+CC	No	194 (19.0)	92 (8.9)	1.100 (0.755-1.602)	1.212 (0.802-1.832)
CT+CC	Yes	349 (34.2)	469 (45.4)	0.388 (0.283-0.532)	*0.532 (0.371-0.762)*
rs6815391 × house type		$OR^{multiply}$ (95% CI)		0.625 (0.523-0.747)	*0.679 (0.554-0.832)*
rs6815391 with ventilation situation					
TT	No	15 (1.5)	9 (0.9)	1.000	1.000
TT	Yes	462 (45.3)	463 (44.8)	0.599 (0.259-1.382)	0.668 (0.268-1.667)
CT+CC	No	23 (2.3)	6 (0.6)	2.300 (0.679-7.796)	1.831 (0.481-6.966)
CT+CC	Yes	520 (51.0)	555 (53.7)	0.562 (0.244-1.296)	0.599 (0.241-1.493)
rs6815391 × ventilation situation		$OR^{multiply}$ (95% CI)		0.896 (0.753-1.065)	*0.791 (0.645-0.969)*
rs6815391 with kitchen ventilator					
TT	No	209 (20.5)	143 (13.8)	1.000	1.000
TT	Yes	268 (26.3)	329 (31.8)	0.557 (0.427-0.728)	0.866 (0.632-1.187)
CT+CC	No	226 (22.2)	164 (15.9)	0.943 (0.704-1.263)	0.834 (0.602-1.156)
CT+CC	Yes	317 (31.1)	397 (38.4)	0.546 (0.422-0.708)	0.823 (0.607-1.114)
rs6815391 × kitchen ventilator		$OR^{multiply}$ (95% CI)		0.722 (0.602-0.867)	0.927 (0.752-1.144)
rs6815391 with COF					
TT	No	89 (8.7)	158 (15.3)	1.000	1.000
TT	Yes	388 (38.0)	314 (30.4)	2.194 (1.626-2.959)	*1.824 (1.308-2.544)*
CT+CC	No	86 (8.4)	179 (17.3)	0.853 (0.592-1.229)	0.812 (0.542-1.216)

Table 5: Continued.

Genotype	Environment	Case (%)	Control (%)	OR (95% CI)	aOR (95% CI)[#]
CT+CC	Yes	457 (44.8)	382 (37.0)	2.124 (1.584-2.847)	*1.716 (1.239-2.375)*
rs6815391 × COF			$OR^{multiply}$ (95% CI)	1.383 (1.159-1.651)	*0.932 (0.876-0.992)*
rs6815391 with smoking					
TT	No	192 (18.8)	265 (25.7)	1.000	1.000
TT	Yes	285 (27.9)	207 (20.0)	1.900 (1.468-2.460)	*1.644 (1.217-2.220)*
CT+CC	No	196 (19.2)	353 (34.2)	0.766 (0.594-0.989)	*0.727 (0.550-0.962)*
CT+CC	Yes	347 (34.0)	208 (20.1)	2.303 (1.788-2.966)	*1.839 (1.372-2.463)*
rs6815391 × smoking			$OR^{multiply}$ (95% CI)	2.045 (1.675-2.497)	*1.650 (1.316-2.069)*
rs6815391 with passive smoking					
TT	No	138 (13.5)	258 (25.0)	1.000	1.000
TT	Yes	339 (33.2)	214 (20.7)	2.962 (2.265-3.873)	*2.373 (1.771-3.180)*
CT+CC	No	173 (17.0)	316 (30.6)	1.024 (0.755-1.351)	0.941 (0.695-1.274)
CT+CC	Yes	370 (36.3)	245 (23.7)	2.823 (2.172-3.670)	*2.092 (1.571-2.787)*
rs6815391 × passive smoking			$OR^{multiply}$ (95% CI)	1.831 (1.511-2.218)	*1.503 (1.216-1.857)*
rs6815391 with drinking alcohol					
TT	No	318 (31.2)	330 (31.9)	1.000	1.000
TT	Yes	159 (15.6)	142 (13.7)	1.162 (0.884-1.528)	0.728 (0.529-1.003)
CT+CC	No	356 (34.9)	419 (40.6)	0.882 (0.715-1.087)	0.817 (0.645-1.034)
CT+CC	Yes	187 (18.3)	142 (13.7)	1.367 (1.046-1.785)	0.831 (0.608-1.137)
rs6815391 × drink alcohol			$OR^{multiply}$ (95% CI)	1.409 (1.111-1.787)	0.978 (0.743-1.287)
rs6815391 with history of lung disease					
TT	No	419 (41.1)	436 (42.2)	1.000	1.000
TT	Yes	58 (5.7)	36 (3.5)	1.676 (1.083-2.595)	1.401 (0.851-2.306)
CT+CC	No	477 (46.8)	520 (50.3)	0.955 (0.795-1.146)	0.888 (0.723-1.090)
CT+CC	Yes	66 (6.5)	41 (4.0)	1.675 (1.109-2.529)	1.560 (0.977-2.490)
rs6815391× history of lung disease			$OR^{multiply}$ (95% CI)	1.674 (1.122-2.496)	*1.633 (1.037-2.570)*
rs6815391 with family history of cancer					
TT	No	385 (37.7)	400 (38.7)	1.000	1.000
TT	Yes	92 (9.0)	72 (7.0)	1.328 (0.946-1.863)	1.350 (0.923-1.975)
CT+CC	No	433 (42.5)	476 (46.1)	0.945 (0.781-1.144)	0.887 (0.715-1.101)
CT+CC	Yes	110 (10.8)	85 (8.2)	1.345 (0.980-1.844)	1.353 (0.949-1.929)
rs6815391 × family history of cancer			$OR^{multiply}$ (95% CI)	1.348 (1.001-1.815)	*1.396 (1.000-1.948)*
rs3740535		$N = 1048$	$N = 1079$		
rs3740535 with pollution near the place of residence					
GG	No	464 (44.3)	561 (52.0)	1.000	1.000
GG	Yes	138 (13.2)	53 (4.9)	3.148 (2.241-4.422)	*2.846 (1.969-4.115)*
GA+AA	No	376 (35.9)	431 (39.9)	1.055 (0.877-1.269)	0.971 (0.789-1.194)
GA+AA	Yes	70 (6.7)	34 (3.2)	2.489 (1.623-3.818)	*2.045 (1.276-3.278)*
rs3740535 × pollution near the place of residence			$OR^{multiply}$ (95% CI)	2.200 (1.447-3.344)	*1.873 (1.180-2.973)*
rs3740535 with house type					
GG	No	204 (19.5)	85 (7.9)	1.000	1.000
GG	Yes	398 (38.0)	529 (49.0)	0.313 (0.236-0.417)	*0.398 (0.288-0.548)*
GA+AA	No	151 (14.4)	93 (8.6)	0.677 (0.471-0.971)	*0.618 (0.415-0.920)*

Table 5: Continued.

Genotype	Environment	Case (%)	Control (%)	OR (95% CI)	aOR (95% CI)[#]
GA+AA	Yes	295 (28.1)	372 (34.5)	0.330 (0.246-0.444)	*0.425 (0.305-0.593)*
rs3740535 × house type			$OR^{multiply}$ (95% CI)	0.745 (0.619-0.895)	0.845 (0.686-1.040)
rs3740535 with ventilation situation					
GG	No	21 (2.0)	10 (0.9)	1.000	1.000
GG	Yes	581 (55.4)	604 (56.0)	0.458 (0.214-0.981)	0.529 (0.227-1.228)
GA+AA	No	18 (1.7)	6 (0.6)	1.429 (0.434-4.705)	1.127 (0.309-4.108)
GA+AA	Yes	428 (40.8)	459 (42.5)	0.444 (0.207-0.954)	0.490 (0.210-1.144)
rs3740535 × ventilation situation			$OR^{multiply}$ (95% CI)	0.932 (0.785-1.108)	*0.800 (0.652-0.980)*
rs3740535 with kitchen ventilator					
GG	No	249 (23.8)	162 (15.0)	1.000	1.000
GG	Yes	353 (33.7)	452 (41.9)	0.508 (0.399-0.647)	0.809 (0.608-1.076)
GA+AA	No	201 (19.2)	162 (15.0)	0.807 (0.606-1.075)	0.758 (0.550-1.045)
GA+AA	Yes	245 (23.4)	303 (28.1)	0.526 (0.406-0.682)	0.858 (0.632-1.164)
rs3740535 × kitchen ventilator			$OR^{multiply}$ (95% CI)	0.781 (0.643-0.950)	1.024 (0.819-1.281)
rs3740535 with COF					
GG	No	103 (9.8)	211 (19.6)	1.000	1.000
GG	Yes	499 (47.6)	403 (37.3)	2.537 (1.937-3.322)	*2.217 (1.641-2.994)*
GA+AA	No	77 (7.3)	131 (12.1)	1.204 (0.834-1.738)	1.272 (0.846-1.911)
GA+AA	Yes	369 (35.2)	334 (31.0)	2.263 (1.714-2.989)	*1.895 (1.387-2.590)*
rs3740535 × COF			$OR^{multiply}$ (95% CI)	1.212 (1.012-1.453)	0.965 (0.907-1.027)
rs3740535 with smoking					
GG	No	246 (23.5)	361 (33.5)	1.000	1.000
GG	Yes	356 (34.0)	253 (23.4)	2.065 (1.643-2.595)	*1.729 (1.322-2.261)*
GA+AA	No	154 (14.7)	274 (25.4)	0.825 (0.639-1.065)	0.806 (0.608-1.069)
GA+AA	Yes	292 (27.9)	191 (17.7)	2.243 (1.758-2.863)	*1.861 (1.395-2.482)*
rs3740535 × smoking			$OR^{multiply}$ (95% CI)	1.796 (1.461-2.208)	*1.506 (1.187-1.909)*
rs3740535 with passive smoking					
GG	No	179 (17.1)	350 (32.4)	1.000	1.000
GG	Yes	423 (40.4)	264 (24.5)	3.133 (2.472-3.970)	*2.665 (2.054-3.458)*
GA+AA	No	131 (12.5)	245 (22.7)	1.045 (0.792-1.381)	1.085 (0.801-1.470)
GA+AA	Yes	315 (30.1)	220 (20.4)	2.800 (2.182-3.592)	*2.256 (1.715-2.969)*
rs3740535 × passive smoking			$OR^{multiply}$ (95% CI)	1.678 (1.376-2.046)	*1.424 (1.142-1.774)*
rs3740535 with drink alcohol					
GG	No	392 (37.4)	450 (41.7)	1.000	1.000
GG	Yes	210 (20.0)	164 (15.2)	1.470 (1.150-1.878)	0.966 (0.725-1.288)
GA+AA	No	292 (27.9)	320 (29.7)	1.048 (0.850-1.290)	1.003 (0.792-1.270)
GA+AA	Yes	154 (14.7)	145 (13.4)	1.219 (0.936-1.588)	0.787 (0.578-1.071)
rs3740535 × drink alcohol			$OR^{multiply}$ (95% CI)	1.110 (0.869-1.417)	0.794 (0.599-1.053)
rs3740535 with history of lung disease					
GG	No	528 (50.4)	564 (52.3)	1.000	1.000
GG	Yes	74 (7.1)	50 (4.6)	1.581 (1.083-2.307)	*1.593 (1.034-2.453)*
GA+AA	No	395 (37.7)	426 (39.5)	0.990 (0.826-1.187)	0.966 (0.787-1.186)
GA+AA	Yes	51 (4.9)	39 (3.6)	1.397 (0.906-2.155)	1.129 (0.693-1.837)
rs3740535× history of lung disease			$OR^{multiply}$ (95% CI)	1.364 (0.891-2.088)	1.110 (0.688-1.790)
rs3740535 with family history of cancer					
GG	No	485 (46.3)	524 (48.6)	1.000	1.000

Table 5: Continued.

Genotype	Environment	Case (%)	Control (%)	OR (95% CI)	aOR (95% CI)[#]
GG	Yes	117 (11.2)	90 (8.3)	1.405 (1.039-1.898)	1.388 (0.989-1.949)
GA+AA	No	352 (33.6)	395 (36.6)	0.963 (0.797-1.164)	0.908 (0.733-1.124)
GA+AA	Yes	94 (9.0)	70 (6.5)	1.451 (1.040-2.024)	*1.515 (1.043-2.200)*
rs3740535 × family history of cancer		$OR^{multiply}$ (95% CI)		1.420 (1.029-1.959)	*1.517 (1.058-2.176)*
rs3130932		$N = 1045$	$N = 1082$		
rs3130932 with pollution near the place of residence					
TT	No	362 (34.6)	418 (38.6)	1.000	1.000
TT	Yes	91 (8.7)	35 (3.2)	3.002 (1.984-4.544)	*2.806 (1.794-4.389)*
GT+GG	No	476 (45.6)	578 (53.4)	0.951 (0.790-1.145)	0.937 (0.762-1.153)
GT+GG	Yes	116 (11.1)	51 (4.7)	2.626 (1.836-3.757)	*2.245 (1.513-3.331)*
rs3130932 × pollution near the place of residence		$OR^{multiply}$ (95% CI)		2.524 (1.795-3.550)	*2.166 (1.489-3.151)*
rs3130932 with house type					
TT	No	149 (14.3)	75 (6.9)	1.000	1.000
TT	Yes	304 (29.1)	378 (34.9)	0.405 (0.295-0.555)	*0.584 (0.408-0.836)*
GT+GG	No	207 (19.8)	103 (9.5)	1.012 (0.703-1.456)	1.099 (0.737-1.638)
GT+GG	Yes	385 (36.8)	526 (48.6)	0.368 (0.271-0.501)	*0.509 (0.359-0.723)*
rs3130932 × house type		$OR^{multiply}$ (95% CI)		0.617 (0.519-0.733)	*0.701 (0.575-0.854)*
rs3130932 with ventilation situation					
TT	No	14 (1.3)	7 (0.6)	1.000	1.000
TT	Yes	439 (42.0)	446 (41.2)	0.492 (0.197-1.231)	0.516 (0.190-1.402)
GT+GG	No	24 (2.3)	8 (0.7)	1.500 (0.447-5.029)	1.086 (0.292-4.045)
GT+GG	Yes	568 (54.4)	621 (57.4)	0.457 (0.183-1.141)	0.473 (0.174-1.282)
rs3130932 × ventilation situation		$OR^{multiply}$ (95% CI)		0.884 (0.745-1.049)	*1.638 (1.149-2.334)*
rs3130932 with kitchen ventilator					
TT	No	204 (19.5)	147 (13.6)	1.000	1.000
TT	Yes	249 (23.8)	306 (28.3)	0.586 (0.448-0.768)	1.036 (0.752-1.427)
GT+GG	No	246 (23.5)	179 (16.5)	0.990 (0.744-1.319)	1.025 (0.744-1.411)
GT+GG	Yes	346 (33.1)	450 (41.6)	0.554 (0.430-0.714)	0.894 (0.662-1.207)
rs3130932 × kitchen ventilator		$OR^{multiply}$ (95% CI)		0.695 (0.583-0.830)	0.872 (0.711-1.070)
rs3130932 with COF					
TT	No	85 (8.1)	150 (13.9)	1.000	1.000
TT	Yes	368 (35.2)	303 (28.0)	2.143 (1.578-2.912)	*1.744 (1.238-2.458)*
GT+GG	No	96 (9.2)	191 (17.7)	0.887 (0.618-1.274)	0.849 (0.568-1.268)
GT+GG	Yes	496 (47.5)	438 (40.5)	1.998 (1.487-2.685)	*1.643 (1.180-2.287)*
rs3130932 × COF		$OR^{multiply}$ (95% CI)		1.328 (1.119-1.577)	0.951 (0.895-1.011)
rs3130932 with smoking					
TT	No	170 (16.3)	268 (24.8)	1.000	1.000
TT	Yes	283 (27.1)	185 (17.1)	2.412 (1.847-3.149)	*2.016 (1.477-2.752)*
GT+GG	No	223 (21.3)	370 (34.2)	0.950 (0.737-1.225)	0.929 (0.702-1.229)
GT+GG	Yes	369 (35.3)	259 (23.9)	2.246 (1.750-2.882)	*1.835 (1.372-2.455)*
rs3130932 × smoking		$OR^{multiply}$ (95% CI)		1.735 (1.436-2.095)	*1.421 (1.145-1.764)*
rs3130932 with passive smoking					
TT	No	133 (12.7)	260 (24.0)	1.000	1.000
TT	Yes	320 (30.6)	193 (17.8)	3.241 (2.467-4.267)	*2.598 (1.921-3.513)*
GT+GG	No	178 (17.0)	340 (31.4)	1.023 (0.776-1.350)	1.006 (0.744-1.361)

Table 5: Continued.

Genotype	Environment	Case (%)	Control (%)	OR (95% CI)	aOR (95% CI)[#]
GT+GG	Yes	414 (39.6)	289 (26.7)	2.800 (2.165-3.622)	*2.237 (1.685-2.970)*
rs3130932 × passive smoking			$OR^{multiply}$ (95% CI)	1.800 (1.499-2.162)	*1.548 (1.263-1.897)*
rs3130932 with drink alcohol					
TT	No	296 (28.3)	325 (30.0)	1.000	1.000
TT	Yes	157 (15.0)	128 (11.8)	1.347 (1.016-1.785)	0.861 (0.621-1.194)
GT+GG	No	385 (36.8)	449 (41.5)	0.941 (0.765-1.159)	0.910 (0.719-1.152)
GT+GG	Yes	207 (19.8)	180 (16.6)	1.263 (0.979-1.628)	0.808 (0.598-1.091)
rs3130932 × drink alcohol			$OR^{multiply}$ (95% CI)	1.238 (0.993-1.544)	0.872 (0.674-1.129)
rs3130932 with history of lung disease					
TT	No	398 (38.1)	417 (38.5)	1.000	1.000
TT	Yes	55 (5.3)	36 (3.3)	1.601 (1.029-2.491)	1.495 (0.909-2.460)
GT+GG	No	524 (50.1)	575 (53.1)	0.955 (0.796-1.145)	0.934 (0.761-1.145)
GT+GG	Yes	68 (6.5)	54 (5.0)	1.319 (0.900-1.935)	1.185 (0.762-1.841)
rs3130932 × history of lung disease			$OR^{multiply}$ (95% CI)	1.412 (1.065-1.871)	1.205 (0.789-1.843)
rs3130932 with family history of cancer					
TT	No	369 (35.3)	387 (35.8)	1.000	1.000
TT	Yes	84 (8.0)	66 (6.1)	1.335 (0.938-1.899)	1.267 (0.855-1.878)
GT+GG	No	467 (44.7)	534 (49.4)	0.917 (0.759-1.108)	0.877 (0.708-1.085)
GT+GG	Yes	125 (12.0)	95 (8.8)	1.380 (1.020-1.867)	*1.462 (1.037-2.061)*
rs3130932 × family history of cancer			$OR^{multiply}$ (95% CI)	1.412 (1.065-1.871)	*1.537 (1.117-2.116)*

[#]By the degree of education, marital status, BMI, pollution near the place of residence, house type, ventilation situation, COF, kitchen ventilator, smoking, passive smoking, drink alcohol, history of lung disease, and family history of cancer adjusted. OR and its interval shown in italic font to represent the $P < 0.05$.

cells. Some scholars [29] have found a novel mechanism between *OCT4* and *REX1* in which Drp1 fission activity partially contributes to the pluripotency in hESCs (human embryonic stem cells). *REX1* achieves mitochondrial fission by reducing the reprogramming barrier (growth stagnation and apoptosis), as well as the process of converting from oxidative phosphorylation to glycolytic metabolism, which depends on the cyclin B1/B2-DRP1 pathway, altering cell cycle progression and the metabolism state to allow stem cells to enter and exit pluripotency [30].

Studies on the association between the *REX1* gene and tumors are rare. The current study found no association between *REX1* rs6815391 polymorphism and lung cancer susceptibility. The stratified analysis of different pathological types of adenocarcinoma also showed no significant difference. However, our results suggested that the TT genotype may be associated with other risks of lung cancer, such as pollution near the place of residence, house type, ventilation situation, COF, smoking, passive smoking, lung disease history, and family history of cancer.

OCT4 is encoded by Pou5f1 and belongs to the POU (Pit-Oct-Unc) transcription factor family and participates in the regulation of downstream genes by binding an octa-base conserved sequence containing ATGCAAAT [31]. The *OCT4* gene is the "core" of stem cells. Some studies [32] have found that the differentiation and maturation of tumor cells are related to the downregulation of *OCT4* expression. Stem cells can also secrete OCT4 and VEGF to promote the origin of tumor epithelial cells into vascular epithelial cells and form small blood vessels for maintaining the survival of dry cells under hypoxia to induce tumor blood transfer for the foundation of resistance to chemotherapy [33]. Our study found that in adenocarcinoma, *OCT4* rs13409 in a co-dominant model CT genotype showed 0.689-fold the risk of lung cancer in CC carriers (95% CI: 0.536-0.885); in dominant models, the risk of lung cancer in CT+TT carriers was 0.745-fold higher than that of CC carriers (95% CI*:* 0.589-0.941). In all subtypes of lung cancers, the risk of *OCT4* rs13409 CT genotype carriers in the co-dominant genetic model was 0.734-fold that of the CC carriers (95% CI*:* 0.610-0.884), and the risk of CT+TT carriers in the recessive model was 0.781-fold that of the CC carriers (95% CI*:* 0.656-0.930). In squamous carcinoma, the risk of lung cancer in the *OCT4* rs3130932 GG carriers in the recessive model was 1.569-fold as high as that of the GT+TT carriers (95% CI: 1.016-2.425).

After analyzing the interaction between the two genotypes of *OCT4* and environmental factors (pollution near the place of residence, house type, COF, ventilation situation, kitchen ventilator, smoking, passive smoking, alcohol drinking, history of lung disease, and family history of cancer), our results showed that the *OCT4* rs13409 dominant model had a combined effect with these environmental factors,

Table 6: Joint and multiplication interaction between gene recessive model and environmental factors.

Genotype	Environment	Case (%)	Control (%)	OR (95% CI)	aOR (95% CI)[#]
rs13409		$N = 1022$	$N = 1053$		
rs13409 with pollution near the place of residence					
CT+CC	No	736 (72.0)	866 (82.2)	1.000	1.000
CT+CC	Yes	165 (16.1)	78 (7.4)	2.489 (1.869-3.315)	*2.224 (1.624-3.046)*
TT	No	88 (8.6)	103 (9.8)	1.005 (0.744-1.358)	0.909 (0.649-1.272)
TT	Yes	33 (3.2)	6 (0.6)	6.471 (2.697-15.530)	*6.308 (2.516-15.815)*
rs13409 × pollution near the place of residence		$OR^{multiply}$ (95% CI)		5.823 (2.429-13.956)	*5.766 (2.302-14.444)*
rs13409 with house type					
CT+CC	No	303 (29.6)	156 (14.8)	1.000	1.000
CT+CC	Yes	598 (58.5)	788 (74.8)	0.402 (0.302-0.535)	*0.448 (0.328-0.613)*
TT	No	45 (4.4)	17 (1.6)	2.600 (1.046-6.463)	*2.935 (1.131-7.617)*
TT	Yes	76 (7.4)	92 (8.7)	0.404 (0.273-0.598)	*0.401 (0.261-0.617)*
rs13409 × house type		$OR^{multiply}$ (95% CI)		1.009 (0.866-1.175)	0.846 (0.595-1.203)
rs13409 with ventilation situation					
CT+CC	No	31 (3.0)	13 (1.2)	1.000	1.000
CT+CC	Yes	870 (85.1)	931 (88.4)	0.392 (0.204-0.754)	0.509 (0.248-1.045)
TT	No	5 (0.5)	2 (0.2)	1.048 (0.180-6.112)	1.311 (0.194-8.848)
TT	Yes	116 (11.4)	107 (10.2)	0.455 (0.226-0.914)	0.544 (0.252-1.175)
rs13409 × ventilation situation		$OR^{multiply}$ (95% CI)		1.132 (0.857-1.495)	*2.274 (1.095-4.724)*
rs13409 with kitchen ventilator					
CT+CC	No	381 (37.3)	275 (26.1)	1.000	1.000
CT+CC	Yes	520 (50.9)	669 (63.5)	0.561 (0.463-0.680)	0.913 (0.718-1.160)
TT	No	58 (5.7)	40 (3.8)	1.047 (0.680-1.612)	0.934 (0.577-1.512)
TT	Yes	63 (6.2)	69 (6.6)	0.659 (0.453-0.959)	1.046 (0.680-1.608)
rs13409 × kitchen ventilator		$OR^{multiply}$ (95% CI)		0.937 (0.658-1.333)	1.117 (0.752-1.658)
rs13409 with COF					
CT+CC	No	149 (14.6)	311 (29.5)	1.000	1.000
CT+CC	Yes	752 (73.6)	633 (60.1)	2.480 (1.986-3.096)	*2.177 (1.696-2.794)*
TT	No	23 (2.3)	24 (2.3)	2.000 (1.093-3.661)	*2.403 (1.236-4.673)*
TT	Yes	98 (9.6)	85 (8.1)	2.406 (1.696-3.415)	*1.864 (1.260-2.759)*
rs13409 × COF		$OR^{multiply}$ (95% CI)		1.208 (0.891-1.637)	1.015 (0.916-1.124)
rs13409 with smoking					
CT+CC	No	351 (34.3)	561 (53.3)	1.000	1.000
CT+CC	Yes	550 (53.8)	383 (36.4)	2.295 (1.905-2.766)	*1.954 (1.559-2.450)*
TT	No	40 (3.9)	64 (6.1)	0.999 (0.658-1.516)	0.935 (0.592-1.477)
TT	Yes	81 (7.9)	45 (4.3)	2.877 (1.952-4.241)	*2.287 (1.468-3.563)*
rs13409 × smoking		$OR^{multiply}$ (95% CI)		1.928 (1.325-2.086)	1.515 (0.995-2.307)
rs13409 with passive smoking					
CT+CC	No	271 (26.5)	528 (50.1)	1.000	1.000
CT+CC	Yes	630 (61.6)	416 (39.5)	2.951 (2.436-3.574)	*2.403 (1.945-2.969)*
TT	No	36 (3.5)	56 (5.3)	1.253 (0.804-1.925)	1.111 (0.683-1.807)
TT	Yes	85 (8.3)	53 (5.0)	3.125 (2.152-4.537)	*2.445 (1.622-3.684)*
rs13409 × passive smoking		$OR^{multiply}$ (95% CI)		1.712 (1.201-2.440)	1.475 (0.997-2.181)
rs13409 with drink alcohol					
CT+CC	No	598 (58.5)	675 (64.1)	1.000	1.000
CT+CC	Yes	303 (29.6)	269 (25.5)	1.271 (1.043-1.549)	0.829 (0.652-1.052)
TT	No	73 (7.1)	75 (7.1)	1.099 (0.782-1.544)	0.983 (0.669-1.444)

Table 6: Continued.

Genotype	Environment	Case (%)	Control (%)	OR (95% CI)	aOR (95% CI)[#]
TT	Yes	48 (4.7)	34 (3.2)	1.594 (1.013-2.506)	0.992 (0.594-1.659)
rs13409 × drink alcohol		$OR^{multiply}$ (95% CI)		1.477 (0.944-2.312)	1.070 (0.647-1.768)
rs13409 with history of lung disease					
CT+CC	No	793 (77.6)	859 (81.6)	1.000	1.000
CT+CC	Yes	108 (10.6)	85 (8.1)	1.376 (1.019-1.858)	1.289 (0.915-1.816)
TT	No	101 (9.9)	105 (10.0)	1.042 (0.780-1.392)	0.944 (0.682-1.308)
TT	Yes	20 (2.0)	4 (0.4)	5.416 (1.843-15.914)	*4.406 (1.394-13.930)*
rs13409 × history of lung disease		$OR^{multiply}$ (95% CI)		5.235 (1.783-15.368)	*4.313 (1.366-13.620)*
rs13409 with family history of cancer					
CT+CC	No	714 (69.9)	805 (76.4)	1.000	1.000
CT+CC	Yes	187 (18.3)	139 (13.2)	1.517 (1.191-1.931)	*1.522 (1.160-1.998)*
TT	No	101 (9.9)	91 (8.6)	1.251 (0.926-1.690)	1.101 (0.784-1.546)
TT	Yes	20 (2.0)	18 (1.7)	1.253 (0.657-2.387)	1.296 (0.632-2.661)
rs13409 × family history of cancer		$OR^{multiply}$ (95% CI)		1.148 (0.604-2.182)	1.197 (0.584-2.453)
rs6815391		$N = 1020$	$N = 1033$		
rs6815391 with pollution near the place of residence					
TT+CT	No	733 (71.9)	832 (80.5)	1.000	1.000
TT+CT	Yes	182 (17.8)	75 (7.3)	2.754 (2.068-3.669)	*2.474 (1.812-3.377)*
CC	No	88 (8.6)	115 (11.1)	0.869 (0.647-1.166)	1.001 (0.721-1.389)
CC	Yes	17 (1.7)	11 (1.1)	1.754 (0.816-3.769)	1.963 (0.855-4.505)
rs6815391 × pollution near the place of residence		$OR^{multiply}$ (95% CI)		1.575 (0.734-3.379)	1.754 (0.764-4.026)
rs6815391 with house type					
TT+CT	No	302 (29.6)	144 (13.9)	1.000	1.000
TT+CT	Yes	613 (60.1)	763 (73.9)	0.383 (0.306-0.480)	*0.508 (0.391-0.661)*
CC	No	32 (3.1)	21 (2.0)	0.727 (0.405-1.304)	0.844 (0.445-1.602)
CC	Yes	73 (7.2)	105 (10.2)	0.332 (0.232-0.474)	*0.517 (0.344-0.777)*
rs6815391 × house type		$OR^{multiply}$ (95% CI)		0.681 (0.499-0.931)	0.875 (0.616-1.243)
rs6815391 with ventilation situation					
TT+CT	No	36 (3.5)	13 (1.3)	1.000	1.000
TT+CT	Yes	879 (86.2)	894 (86.5)	0.355 (0.187-0.674)	*0.412 (0.204-0.831)*
CC	No	2 (0.2)	2 (0.2)	0.361 (0.046-2.838)	0.193 (0.021-1.757)
CC	Yes	103 (10.1)	124 (12.0)	0.300 (0.151-0.596)	*0.410 (0.193-0.869)*
rs6815391 × ventilation situation		$OR^{multiply}$ (95% CI)		0.823 (0.624-1.086)	1.031 (0.466-2.281)
rs6815391 with kitchen ventilator					
TT+CT	No	402 (39.4)	279 (27.0)	1.000	1.000
TT+CT	Yes	513 (50.3)	628 (60.8)	0.567 (0.468-0.687)	0.910 (0.717-1.155)
CC	No	33 (3.2)	28 (2.7)	0.818 (0.483-1.384)	0.860 (0.478-1.547)
CC	Yes	72 (7.1)	98 (9.5)	0.510 (0.363-0.717)	0.927 (0.627-1.372)
rs6815391 × kitchen ventilator		$OR^{multiply}$ (95% CI)		0.725 (0.528-0.995)	0.994 (0.698-1.415)
rs6815391 with COF					
TT+CT	No	150 (14.7)	290 (28.1)	1.000	1.000
TT+CT	Yes	765 (75.0)	617 (59.7)	2.397 (1.916-2.998)	*1.999 (1.554-2.571)*
CC	No	25 (2.5)	47 (4.5)	1.028 (0.609-1.736)	1.080 (0.614-1.900)

Table 6: Continued.

Genotype	Environment	Case (%)	Control (%)	OR (95% CI)	aOR (95% CI)[#]
CC	Yes	80 (7.8)	79 (7.6)	1.958 (1.355-2.829)	*1.855 (1.232-2.791)*
rs6815391 × COF		$OR^{multiply}$ (95% CI)		1.028 (0.744-1.421)	0.960 (0.872-1.057)
rs6815391 with smoking					
TT+CT	No	349 (34.2)	536 (51.9)	1.000	1.000
TT+CT	Yes	566 (55.5)	371 (35.9)	2.343 (1.942-2.827)	*2.008 (1.596-2.525)*
CC	No	39 (3.8)	82 (7.9)	0.730 (0.487-1.094)	0.858 (0.555-1.328)
CC	Yes	66 (6.5)	44 (4.3)	2.304 (1.537-3.453)	*2.221 (1.417-3.482)*
rs6815391 × smoking		$OR^{multiply}$ (95% CI)		1.555 (1.051-2.301)	1.531 (0.994-2.359)
rs6815391 with passive smoking					
TT+CT	No	273 (26.8)	499 (48.3)	1.000	1.000
TT+CT	Yes	642 (62.9)	408 (39.5)	2.876 (2.372-3.488)	*2.253 (1.822-2.786)*
CC	No	38 (3.7)	75 (7.3)	0.926 (0.610-1.406)	0.895 (0.569-1.409)
CC	Yes	67 (6.6)	51 (4.9)	2.401 (1.621-3.557)	*2.356 (1.530-3.629)*
rs6815391 × passive smoking		$OR^{multiply}$ (95% CI)		1.354 (0.930-1.970)	*1.516 (1.000-2.300)*
rs6815391 with drink alcohol					
TT+CT	No	603 (59.1)	658 (63.7)	1.000	1.000
TT+CT	Yes	312 (30.6)	249 (24.1)	1.367 (1.120-1.670)	0.874 (0.686-1.112)
CC	No	71 (7.0)	91 (8.8)	0.851 (0.612-1.184)	0.981 (0.678-1.420)
CC	Yes	34 (3.3)	35 (3.4)	1.060 (0.653-1.721)	0.833 (0.484-1.435)
rs6815391 × drink alcohol		$OR^{multiply}$ (95% CI)		0.983 (0.608-1.589)	0.877 (0.515-1.496)
rs6815391 with history of lung disease					
TT+CT	No	800 (78.4)	841 (81.4)	1.000	1.000
TT+CT	Yes	115 (11.3)	66 (6.4)	1.832 (1.333-2.517)	*1.702 (1.186-2.445)*
CC	No	96 (9.4)	115 (11.1)	0.878 (0.658-1.170)	1.032 (0.748-1.424)
CC	Yes	9 (0.9)	11 (1.1)	0.860 (0.355-2.087)	0.906 (0.340-2.416)
rs6815391 × history of lung disease		$OR^{multiply}$ (95% CI)		0.827 (0.341-2.004)	0.853 (0.320-2.277)
rs6815391 with family history of cancer					
TT+CT	No	736 (72.2)	768 (74.3)	1.000	1.000
TT+CT	Yes	179 (17.5)	139 (13.5)	1.344 (1.053-1.714)	*1.409 (1.072-1.852)*
CC	No	82 (8.0)	108 (10.5)	0.792 (0.584-1.074)	0.940 (0.670-1.319)
CC	Yes	23 (2.3)	18 (1.7)	1.333 (0.714-2.491)	1.614 (0.795-3.274)
rs6815391 × family history of cancer		$OR^{multiply}$ (95% CI)		1.301 (0.698-2.425)	1.535 (0.758-3.106)
rs3740535		$N = 1048$	$N = 1079$		
rs3740535 with pollution near the place of residence					
GA+GG	No	779 (74.3)	934 (86.6)	1.000	1.000
GA+GG	Yes	196 (18.7)	81 (7.5)	2.901 (2.202-3.823)	*2.669 (1.976-3.605)*
AA	No	61 (5.8)	58 (5.4)	1.261 (0.869-1.829)	1.188 (0.784-1.800)
AA	Yes	12 (1.1)	6 (0.6)	2.398 (0.896-6.419)	1.624 (0.537-4.911)
rs3740535 × pollution near the place of residence		$OR^{multiply}$ (95% CI)		2.071 (0.775-5.540)	1.419 (0.470-4.289)
rs3740535 with house type					
GA+GG	No	322 (30.7)	166 (15.4)	1.000	1.000
GA+GG	Yes	653 (62.3)	849 (78.7)	0.397 (0.320-0.491)	*0.516 (0.403-0.661)*
AA	No	33 (3.1)	12 (1.1)	1.418 (0.713-2.817)	1.232 (0.578-2.624)

Table 6: Continued.

Genotype	Environment	Case (%)	Control (%)	OR (95% CI)	aOR (95% CI)[#]
AA	Yes	40 (3.8)	52 (4.8)	0.397 (0.252-0.624)	*0.546 (0.331-0.898)*
rs3740535 × house type		$OR^{multiply}$ (95% CI)		0.784 (0.514-1.194)	0.875 (0.548-1.395)
rs3740535 with ventilation situation					
GA+GG	No	37 (3.5)	13 (1.2)	1.000	1.000
GA+GG	Yes	938 (89.5)	1002 (92.9)	0.329 (0.174-0.623)	*0.384 (0.191-0.773)*
AA	No	2 (0.2)	3 (0.3)	0.234 (0.035-1.562)	*0.109 (0.013-0.925)*
AA	Yes	71 (6.8)	61 (5.7)	0.409 (0.199-0.839)	*0.450 (0.204-0.992)*
rs3740535 × ventilation situation		$OR^{multiply}$ (95% CI)		1.213 (0.852-1.727)	1.476 (0.475-4.529)
rs3740535 with kitchen ventilator					
GA+GG	No	400 (38.2)	305 (28.3)	1.000	1.000
GA+GG	Yes	575 (54.9)	710 (65.8)	0.618 (0.513-0.743)	1.013 (0.804-1.275)
AA	No	50 (4.8)	19 (1.8)	2.007 (1.159-3.474)	*2.027 (1.170-3.730)*
AA	Yes	23 (2.2)	45 (4.2)	0.390 (0.231-0.658)	0.656 (0.366-1.178)
rs3740535 × kitchen ventilator		$OR^{multiply}$ (95% CI)		0.516 (0.310-0.858)	0.641 (0.365-1.123)
rs3740535 with COF					
GA+GG	No	170 (16.2)	321 (29.7)	1.000	1.000
GA+GG	Yes	805 (76.8)	694 (64.3)	2.190 (1.772-2.707)	*1.851 (1.458-2.349)*
AA	No	10 (1.0)	21 (1.9)	0.899 (0.414-1.953)	0.887 (0.386-2.039)
AA	Yes	63 (6.0)	43 (4.0)	2.766 (1.800-4.253)	*2.163 (1.329-3.521)*
rs3740535 × COF		$OR^{multiply}$ (95% CI)		1.541 (1.036-2.293)	1.017 (0.895-1.155)
rs3740535 with smoking					
GA+GG	No	376 (35.9)	595 (55.1)	1.000	1.000
GA+GG	Yes	599 (57.2)	420 (38.9)	2.257 (1.886-2.701)	*1.900 (1.525-2.367)*
AA	No	24 (2.3)	40 (3.7)	0.949 (0.563-1.601)	0.903 (0.510-1.598)
AA	Yes	49 (4.7)	24 (2.2)	3.231 (1.950-5.354)	*2.539 (1.442-4.471)*
rs3740535 × smoking		$OR^{multiply}$ (95% CI)		2.156 (1.313-3.540)	*1.781 (1.024-3.100)*
rs3740535 with passive smoking					
GA+GG	No	283 (27.0)	557 (51.6)	1.000	1.000
GA+GG	Yes	692 (66.0)	458 (42.4)	2.974 (2.470-3.580)	*2.406 (1.961-2.952)*
AA	No	27 (2.6)	38 (3.5)	1.398 (0.837-2.337)	1.133 (0.641-2.005)
AA	Yes	46 (4.4)	26 (2.4)	3.48 2 (2.108-5.751)	*2.591 (1.495-4.489)*
rs3740535 × passive smoking		$OR^{multiply}$ (95% CI)		1.859 (1.141-3.031)	1.560 (0.909-2.679)
rs3740535 with drink alcohol					
GA+GG	No	636 (60.7)	719 (66.6)	1.000	1.000
GA+GG	Yes	339 (32.3)	296 (27.4)	1.295 (1.072-1.564)	0.847 (0.673-1.064)
AA	No	48 (4.6)	51 (4.7)	1.064 (0.707-1.601)	0.906 (0.569-1.443)
AA	Yes	25 (2.4)	13 (1.2)	2.174 (1.103-4.285)	1.566 (0.731-3.355)
rs3740535 × drink alcohol		$OR^{multiply}$ (95% CI)		2.004 (1.020-3.938)	1.683 (0.791-3.577)
rs3740535 with history of lung disease					
GA+GG	No	859 (82.0)	935 (86.7)	1.000	1.000
GA+GG	Yes	116 (11.1)	80 (7.4)	1.578 (1.170-2.129)	*1.467 (1.043-2.064)*
AA	No	64 (6.1)	55 (5.1)	1.267 (0.873-1.838)	1.199 (0.786-1.829)
AA	Yes	9 (0.9)	9 (0.8)	1.088 (0.430-2.755)	0.920 (0.320-2.644)
rs3740535 × history of lung disease		$OR^{multiply}$ (95% CI)		1.030 (0.407-2.605)	0.880 (0.306-2.529)

Table 6: Continued.

Genotype	Environment	Case (%)	Control (%)	OR (95% CI)	aOR (95% CI)[#]
rs3740535 with family history of cancer					
GA+GG	No	783 (74.7)	866 (80.3)	1.000	1.000
GA+GG	Yes	192 (18.3)	149 (13.8)	1.425 (1.127-1.802)	*1.551 (1.191-2.019)*
AA	No	54 (5.2)	53 (4.9)	1.127 (0.762-1.666)	1.209 (0.779-1.874)
AA	Yes	19 (1.8)	11 (1.0)	1.910 (0.903-4.040)	1.189 (0.517-2.738)
rs3740535 × family history of cancer		$OR^{multiply}$ (95% CI)		1.793 (0.849-3.786)	1.094 (0.476-2.510)
rs3130932		$N = 1045$	$N = 1082$		
rs3130932 with pollution near the place of residence					
GT+TT	No	728 (69.7)	867 (80.1)	1.000	1.000
GT+TT	Yes	185 (17.7)	80 (7.4)	2.754 (2.081-3.645)	*2.418 (1.780-3.284)*
GG	No	110 (10.5)	129 (11.9)	1.016 (0.773-1.334)	1.028 (0.757-1.396)
GG	Yes	22 (2.1)	6 (0.6)	4.367 (1.761-10.827)	*4.881 (1.849-12.885)*
rs3130932 × pollution near the place of residence		$OR^{multiply}$ (95% CI)		3.857 (1.557-9.550)	*4.354 (1.649-11.495)*
rs3130932 with house type					
GT+TT	No	302 (28.9)	153 (14.1)	1.000	1.000
GT+TT	Yes	611 (58.5)	794 (73.4)	0.390 (0.312-0.486)	*0.542 (0.419-0.701)*
GG	No	54 (5.2)	25 (2.3)	1.094 (0.656-1.827)	1.433 (0.817-2.513)
GG	Yes	78 (7.5)	110 (10.2)	0.359 (0.253-0.509)	*0.535 (0.360-0.795)*
rs3130932 × house type		$OR^{multiply}$ (95% CI)		0.713 (0.526-0.965)	0.832 (0.591-1.171)
rs3130932 with ventilation situation					
GT+TT	No	34 (3.3)	14 (1.3)	1.000	1.000
GT+TT	Yes	879 (84.1)	933 (86.2)	0.388 (0.207-0.728)	*0.503 (0.253-0.998)*
GG	No	4 (0.4)	1 (0.1)	1.647 (0.169-16.070)	2.456 (0.214-28.192)
GG	Yes	128 (12.2)	134 (12.4)	0.393 (0.202-0.767)	0.534 (0.257-1.110)
rs3130932 × ventilation situation		$OR^{multiply}$ (95% CI)		0.988 (0.762-1.279)	1.063 (0.500-2.262)
rs3130932 with kitchen ventilator					
GT+TT	No	396 (37.9)	286 (26.4)	1.000	1.000
GT+TT	Yes	517 (49.5)	661 (61.1)	0.565 (0.467-0.684)	0.926 (0.730-1.173)
GG	No	54 (5.2)	40 (3.7)	0.975 (0.630-1.508)	1.045 (0.646-1.689)
GG	Yes	78 (7.5)	95 (8.8)	0.593 (0.424-0.830)	1.040 (0.704-1.537)
rs3130932 × kitchen ventilator		$OR^{multiply}$ (95% CI)		0.838 (0.613-1.145)	1.093 (0.767-1.559)
rs3130932 with COF					
GT+TT	No	162 (15.5)	297 (27.4)	1.000	1.000
GT+TT	Yes	751 (71.9)	650 (60.1)	2.118 (1.703-2.635)	*1.823 (1.426-2.332)*
GG	No	19 (1.8)	44 (4.1)	0.792 (0.447-1.401)	1.017 (0.547-1.892)
GG	Yes	113 (10.8)	91 (8.4)	2.277 (1.627-3.185)	*2.007 (1.378-2.923)*
rs3130932 × COF		$OR^{multiply}$ (95% CI)		1.320 (0.988-1.765)	1.013 (0.922-1.112)
rs3130932 with smoking					
GT+TT	No	341 (32.6)	557 (51.5)	1.000	1.000
GT+TT	Yes	572 (54.7)	390 (36.0)	2.396 (1.988-2.886)	*2.016 (1.607-2.529)*
GG	No	52 (5.0)	81 (7.5)	1.049 (0.722-1.523)	1.144 (0.759-1.724)
GG	Yes	80 (7.7)	54 (5.0)	2.420 (1.671-3.505)	*2.113 (1.389-3.212)*
rs3130932 × smoking		$OR^{multiply}$ (95% CI)		1.578 (1.105-2.253)	1.414 (0.950-2.106)

Table 6: Continued.

Genotype	Environment	Case (%)	Control (%)	OR (95% CI)	aOR (95% CI)[#]
rs3130932 with passive smoking					
GT+TT	No	273 (26.1)	519 (48.0)	1.000	1.000
GT+TT	Yes	640 (61.2)	428 (39.6)	2.843 (2.349-3.441)	*2.296 (1.859-2.834)*
GG	No	38 (3.6)	81 (7.5)	0.892 (0.591-1.347)	0.934 (0.597-1.460)
GG	Yes	94 (9.0)	54 (5.0)	*3.309 (2.297-4.769)*	*2.835 (1.899-4.233)*
rs3130932 × passive smoking		$OR^{multiply}$ (95% CI)		1.882 (1.331-2.660)	1.778 (1.214-2.604)
rs3130932 with drink alcohol					
GT+TT	No	592 (56.7)	678 (62.7)	1.000	1.000
GT+TT	Yes	321 (30.7)	269 (24.9)	1.367 (1.123-1.663)	0.882 (0.696-1.119)
GG	No	89 (8.5)	96 (8.9)	1.062 (0.780-1.446)	1.111 (0.785-1.573)
GG	Yes	43 (4.1)	39 (3.6)	1.263 (0.807-1.975)	0.934 (0.560-1.557)
rs3130932 × drink alcohol		$OR^{multiply}$ (95% CI)		1.148 (0.738-1.786)	0.968 (0.586-1.598)
rs3130932 with history of lung disease					
GT+TT	No	805 (77.0)	872 (80.6)	1.000	1.000
GT+TT	Yes	108 (10.3)	75 (6.9)	1.560 (1.144-2.126)	*1.478 (1.037-2.105)*
GG	No	117 (11.2)	120 (11.1)	1.056 (0.805-1.386)	1.165 (0.857-1.583)
GG	Yes	15 (1.4)	15 (1.4)	1.083 (0.526-2.230)	0.962 (0.421-2.196)
rs3130932 × history of lung disease		$OR^{multiply}$ (95% CI)		1.036 (0.504-2.130)	0.914 (0.401-2.085)
rs3130932 with family history of cancer					
GT+TT	No	731 (70.0)	809 (74.8)	1.000	1.000
GT+TT	Yes	182 (17.4)	138 (12.8)	1.460 (1.145-1.861)	*1.484 (1.129-1.950)*
GG	No	105 (10.0)	112 (10.3)	1.038 (0.781-1.379)	1.093 (0.793-1.507)
GG	Yes	27 (2.6)	23 (2.1)	1.299 (0.738-2.286)	1.632 (0.862-3.092)
rs3130932 × family history of cancer		$OR^{multiply}$ (95% CI)		1.221 (0.696-2.144)	1.520 (0.805-2.873)

[#]By the degree of education, marital status, BMI, pollution near the place of residence, house type, ventilation situation, COF, kitchen ventilator, smoking, passive smoking, drink alcohol, history of lung disease, and family history of cancer adjusted. OR and its interval shown in italic font to represent the $P < 0.05$.

Table 7: Smoking interaction with four gene loci.

		RERI	*AP*	*S*
rs13409 dominant genetic model	Smoking	0.047 (-1.232-1.325)	0.010 (-0.264-0.284)	1.013 (0.712-1.441)
rs13409 recessive genetic model	Smoking	-0.638 (-2.689-1.412)	-0.160 (-0.658-0.338)	0.824 (0.478-1.422)
rs3130932 dominant genetic model	Smoking	0.303 (-0.805-1.411)	0.074 (-0.186-0.333)	1.108 (0.761-1.611)
rs3130932 recessive genetic model	Smoking	-0.107 (-1.673-1.459)	-0.031 (-0.488-0.425)	0.958 (0.516-1.776)
rs3740535 dominant genetic model	Smoking	-0.460 (–1.662-0.742)	-0.116 (-0.428-0.195)	0.866 (0.601-1.247)
rs3740535 recessive genetic model	Smoking	-1.240 (-4.376-1.896)	-0.306 (-1.036-0.423)	0.711 (0.359-1.409)
rs6815391 dominant genetic model	Smoking	-1.007 (-2.298-0.284)	-0.247 (-0.584-0.090)	0.754 (0.532-1.067)
rs6815391 recessive genetic model	Smoking	-0.657 (-2.855-1.541)	-0.154 (-656-0.349)	0.833 (0.483-1.437)

Table 8: Multivariate analysis.

Variable	*B*	*P*	OR (OR 95% CI)
Junior and senior high school	0.125	0.442	1.133 (0.824-1.556)
College degree or above	-0.329	0.036	*0.719 (0.529-0.978)*
Others (marital status)	1.889	0.006	*6.615 (1.704-25.678)*
Single (marital status)	1.813	0.012	*6.126 (1.495-25.101)*
18.5 < BMI < 23.9	1.300	<0.001	*3.674 (2.487-5.419)*
BMI ≥ 24	0.512	<0.001	*1.669 (1.365-2.041)*
Building (with cottage ratio)	0.409	0.436	1.505 (0.538-4.209)
Ventilation general	-0.805	0.014	*0.447 (0.235-0.851)*
Ventilation worse	-0.103	0.767	0.902 (0.455-1.787)
Not pollution near the place of residence	-0.843	<0.001	*0.430 (0.325-0.569)*
Kitchen ventilator	-0.051	0.648	0.950 (0.764-1.182)
Much fumes	1.115	<0.001	*3.049 (1.674-5.556)*
Some fumes	0.535	<0.001	*1.708 (1.278-2.282)*
Little fumes	0.630	<0.001	*1.877 (1.485-2.373)*
Smoking	0.653	<0.001	*1.921 (1.564-2.360)*
Passive smoking	0.865	<0.001	*2.374 (1.959-2.878)*
History of lung disease	0.333	0.037	*1.394 (1.020-1.907)*
Family history of cancer	0.348	0.006	*1.417 (1.106-1.814)*
Drink alcohol	-0.104	0.349	0.901 (0.725-1.120)
1 protected genotypes	-0.486	0.006	*0.615 (0.436-0.868)*
2 protected genotypes	-0.291	0.030	*0.747 (0.575-0.972)*
3 protected genotypes	-0.154	0.199	0.857 (0.677-1.085)

[#]OR and its interval shown in italic font to represent the $P < 0.05$.

while two genotypes of *OCT4* in the recessive model had an interaction with the environmental factors except for alcohol drinking and kitchen ventilator. The *OCT4* rs3130932 dominant model interacted with these environmental factors with the exception of alcohol drinking, kitchen ventilator, and history of lung disease. The *OCT4* rs13409CC and *OCT4* rs3130932GG genotypes were also found to be risk factors for lung cancer. *OCT4* rs13409 showed [34] a significant association with multiple myeloma risk in 1,832 controls and 2,894 MM from seven European countries and Israel. In northern Iran [35], the *OCT4* rs3130932G allele was associated with the incidence of gastric cancer; genotypes AC [$P = 0.031$, OR = 0.63 (0.44-0.91)] and AC+CC [$P = 0.031$, OR = 0.68 (0.48-0.95)] had protective effects on patients in north India [36]. In Greece [37], however, there was no significant association between the genotype tested and the risk of breast, ovarian, or lung cancer.

Vertebrates contain two different *CTBP2* genes, which are located on human chromosomes 4p16 and l0q26.13, encoding CTBP1 and CTBP2 proteins, and both are structurally highly homologous [38]. A variety of transcription factors interact directly or indirectly with *CTBP*, and some of these are related to stem cell maintenance or development [39]. *CTBP2* is a transcriptional corepressor and a regulator during exit from pluripotency [40]. *CTBP2* binds transcription factors through a Pro-X-Asp-Leu-Ser motif and recruits epigenetic remodelers to form the complex [41]. The overexpression of the *CtBP2* protein in NSCLC tissues indicates that *CtBP2* is closely related to the occurrence of NSCLC, especially in the lung adenocarcinoma tissues, which is 100% overexpressed, indicating that *CtBP2* is highly likely to play an important role in the occurrence and development of lung adenocarcinoma [42]. *CTBP2* knockdown results in the activation of p53-dependent apoptosis arrest [43]. A recent study [44] showed that *CTBP2* regulates deacetylation of H3K27 to fine control the withdrawal of pluripotency. One of the Ctbp2-binding zinc finger proteins, Zfp217, is known as an oncogenic protein associated with various cancers [45]. *Ctbp2* binds to the enhancers and promoters of actively transcribed genes in undifferentiated ESCs that *Ctbp2* associates with core components of NuRD and *Oct4*. These results suggest that *Ctbp2* regulates ESC fate by binding to actively transcribed genes [46]. Also, *CTBP2* plays a role in cell migration, signal pathways, and the cell cycle. Previous reports indicated that *CtBP2* could promote H1299 lung cancer cell migration via repressing PTEN expression and stimulating phosphatidylinositol 3-kinase activity, thereby promoting cell migration [47]. Its overexpression could not only repress the epithelial marker E-cadherin but also upregulate the mesenchymal marker N-cadherin as well as vimentin to enhance migration [48]; in lung cancer cells, it can inhibit the Wnt signaling pathway to promote cell apoptosis and affect the cell cycle [25].

This study found that the genotype frequency distribution of *CTBP2* rs3740535 was different between the patient group and the control group. The dominant or recessive genetic model showed that the risk of lung cancer was increased when combined with pollution near the place of residence, house type, COF, ventilation situation, smoking, passive smoking, history of lung disease, or family history of cancer.

Our results showed the combined effect of the four genotypes with the environmental factors of pollution near the place of residence, worse ventilation situation, smoking, passive smoking, COF, and family history of cancer. These factors together increase the risk of lung cancer in the population. We did not see an additive interaction between the four locus polymorphisms and smoking. The genotypes were related to the survival outcome of lung cancer patients. The number of protective genotypes of the four loci divided into different groups to evaluate its combined effect with the factors influencing lung cancer in the univariate analysis was also included in the logistic multivariate analysis. Our results showed that unmarried status, BMI, COF, smoking, passive smoking, family history of cancer, and history of lung disease were independent risk factors of lung cancer; college degree or above, no pollution near the place of residence, 1 or 2 protective genotypes, and well ventilation can reduce the occurrence of lung cancer.

The sample size was large, and the power of the results was high in the current study. However, our study had limitations. First, we could not completely rule out selection bias, although this was one of the objectives of using three of the largest flow hospitals. Second, the functional studies should

be confirmed. Third, environmental factors were significantly different between the two groups, so the relationship between lung cancer and SNPs could not be directly determined. Therefore, the multivariate regression analysis was used for removing the influence of confounders and to explore the relationship between SNPs and lung cancer.

5. Conclusion

In conclusion, our study indicated that the *OCT4* rs13409 locus was associated with susceptibility to lung cancer, and *OCT4* rs13409 CC genotype carriers showed an increased risk of lung adenocarcinoma, whereas *OCT4* rs3130932 GG carriers showed an increased risk of squamous carcinoma. However, the conclusion should be further demonstrated in a larger sample size.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

This study was approved by the Institutional Review Board of Fujian Medical University (Fuzhou, China), and all participants signed informed consent forms.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

SQ carried out the experiments and helped draft the manuscript. LZQ, XQP, and QML carried out the experiments and collected the samples. HZJ and WWX participated in the design of the study and performed the statistical analysis. HF and LC conceived of the study and participated in its design and coordination and helped draft the manuscript. All authors read and approved the final manuscript.

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Supplementary Materials

Supplementary Table 1: The genomic location of the four SNPs. *(Supplementary Materials)*

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