LRBA Gene Polymorphisms and Risk of Coal Workers’ Pneumoconiosis: A Case–Control Study from China

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Abstract: The lipopolysaccharide (LPS)-responsive beige-like anchor protein (LRBA) is a member of the WDL-BEACH-WD (WBW) gene family. Defects in this gene are associated with the disordered autoimmunity in various diseases, including pulmonary fibrosis. In this study, we investigated the association between the functional polymorphisms in LRBA and risk of coal workers’ pneumoconiosis (CWP) in a Chinese population. Three potentially functional polymorphisms (rs2290846, rs3749574, and rs1782360) in LRBA were genotyped and analyzed in a case–control study, including 703 CWP cases and 705 controls. Genotyping was performed by the ABI 7900HT Real Time PCR system. Our results suggested that genotype rs2290846 AA was significantly associated with decreased risk of CWP (Adjusted OR = 0.61, 95% CI = 0.41–0.92), and the recessive model also supported the protective role of the genotype (Adjusted OR = 0.60, 95% CI = 0.40–0.89). Further, the polymorphism of rs2290846 decreased the CWP risk among cases over 27 years of dust exposure (adjusted OR = 0.51, 95% CI = 0.28–0.94) and non-smokers (adjusted OR = 0.58, 95% CI = 0.34–1.00). A potential role of rs2290846 AA has been proposed by expression quantitative trait loci (eQTL) and The Cancer Genome Atlas (TCGA). The present results suggest that LRBA SNPs are associated with CWP susceptibility in a Chinese population. Further studies focused on detailed mechanism or larger cohorts are warranted to validate our findings.

Keywords: LRBA; polymorphisms; coal workers’ pneumoconiosis; genetics

1. Introduction

Pneumoconiosis is a group of occupational lung fibrotic diseases which is primarily caused by exposure to inorganic dust particulates which are retained in the lung parenchyma, such as crystalline silica, asbestos, and coal dust [1]. Pneumoconiosis has been the major occupational disease in China in the past 60 years and presently, accounting for more than 70% of new cases annually. As reported in 2014, 89.66% of the total 29,972 reported occupational cases was pneumoconiosis, among which coal workers’ pneumoconiosis (CWP) and silicosis accounted for 51.5% and 42.7%, respectively [2]. CWP is a kind of incurable and progressive disease, characterized by chronic lung inflammation and the formation of fibrotic lesions which result from the inhalation of airborne coal mining dust containing free crystalline silica [3]. Although strong evidence showed that various cytokines and the extracellular matrix (ECM) are involved in the CWP process [4], the pathogenesis and influencing factors of CWP are not entirely clear.
The pathogenesis of pulmonary fibrosis is quite complex, since numerous molecular pathways and cell types are involved in the process. Activated inflammatory cells, vascular leak, and released profibrotic cytokines create a supportive environment for exaggerated fibroblast and myofibroblast activity [5]. Various cell types participate in this progress, including macrophages, T lymphocytes, vascular endothelial cells, epithelial cells, myofibroblasts, and so on [6]. Altered levels of serum immunoglobulins have been found in CWP since the 1980s [7]. Previous studies proved that abnormalities in T lymphocytes may play an important role in pulmonary fibrosis [8]. T cells could regulate fibrosis by producing cytokines. Treatment with anti-CD4 antibodies reduces the severity of fibrosis, while IL-10 helps limit the silica-induced inflammatory response but amplifies the fibrotic response [9,10]. Additionally, lymphocyte–monocyte interactions have been identified as crucial pathological processes in fibrotic diseases [11].

Autophagy is a highly conserved fundamental mechanism which is mainly involved in the clearance of damaged organelles and proteins to maintain cellular homeostasis [12,13]. Cytosolic substrates are assimilated in autophagosomes and then transferred to endosomes or lysosomes for further digestion, which is induced by lysosomal hydrolases [14]. Studies have proved that autophagy plays an important role in the processes of various diseases, including cancer, diabetes, and fibrosis [15–17]. A recent study showed that autophagosomes accumulated in alveolar macrophages of human silicosis [18], and also our previous study proved that autophagy is involved in the development of silica-induced pulmonary fibrosis [19].

Mutations in the “lipopolysaccharide (LPS)-responsive beige-like anchor protein” (LRBA) gene cause a syndrome of autoimmunity, lymphoproliferation, and humoral immune deficiency [20]. Meanwhile, LRBA plays a key role in autophagy and T-cell deficiency [21,22]. Germline mutations have been found in the LRBA gene, which could affect its function by abolishing the expression of LRBA protein [23]. Although it is quite clear that LRBA could regulate autophagy and T-cell function, whether the genetic variations of LRBA are associated with the risk of CWP has not yet been explored. In this study, we investigated the potential role of LRBA polymorphisms in CWP by a Chinese population to better understand the genetic susceptibility of CWP.

2. Materials and Methods

2.1. Study Subjects

This research was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Nanjing Medical University (approval code NJMUER201600328). The present case–control study consisted of 703 CWP patients and 705 controls, which were recruited from the coal mines of Xuzhou Mining Business Group Co., Ltd. (Xuzhou, China) between January 2006 and December 2010, as described previously [24]. All subjects are coming from an ethnically homogeneous Chinese population without a genetic relationship who spent their entire working career within the company mentioned above. Subjects were excluded if they had clinical evidence of autoimmune diseases, had received immunosuppressive or immunostimulatory therapy, or were subjected to radiotherapy. High-kilovolt chest X-ray and physical examinations were performed based on the China National Diagnostic Criteria for Pneumoconiosis (GBZ 70-2002) to confirm diagnoses. The pneumoconiosis cases were classified into stage I, stage II, or stage III according to the size, profusion, and distribution range of opacities with agreement by at least two out of three national certified readers. The controls were healthy miners from the same company, matched with the CWP cases for age, dust exposure period, and job types. Through a double-blind method, the questionnaire was done by face-to-face interviewers focused on individual information including age, respiratory symptoms, occupational histories, smoking habits, and others. Blood samples (5 mL) were obtained from all subjects and used for routine lab tests. Written informed consent was obtained from all individuals in this study. Our research protocol was specifically approved by the Institutional
Review Board of Nanjing Medical University. The investigations were carried out following the rules of the Declaration of Helsinki of 1975, revised in 2008.

2.2. SNP Selection

To select the most likely functional single nucleotide polymorphisms (SNPs) influencing LRBA gene, we chose all the SNPs located in the exon as determined in the UCSC Genome Browser (Human GRCh37/hg19). We included the following criteria for SNPs: (i) the SNPs should be located in the exon; (ii) the minor allele frequency (MAF) should be >5% in the Chinese Han Beijing population (CHB); and (iii) the SNPs should be non-synonymous. At last, three SNPs (rs2290846, rs3749574, rs1782360) located in the exon region were included in the study, which were likely to regulate the transcription of LRBA.

2.3. Genotyping

The genomic DNA was isolated from the peripheral blood samples of the study subjects using the conventional phenol-chloroform method. A 7900HT Real Time PCR system (Applied Biosystems, Foster City, CA, USA) was used to perform genotyping, according to the manufacturer’s protocols. The sequences of primer and probe for each SNP are available on request (BioSteed BioTechnologies Co., Ltd., Nanjing, China). The amplification was performed in a total volume of 5 µL, 50 ng genomic DNA was used for each reaction, and amplification was performed under the following conditions: 50 °C for 2 min and 95 °C for 10 min followed by 45 cycles of 95 °C for 15 s and 60 °C for 1 min. Negative controls were included in each plate to ensure accuracy of the genotyping. Ten percent of the samples were randomly selected for confirmation, and the results were 100% concordant. For quality control, genotyping was performed by two researchers in a blinded fashion. Genotyping was conducted by two researchers independently in a blinded fashion without knowledge of the workers’ personal details or case status.

2.4. Bioinformatical Analysis and Gene Expression Levels

Data from the Genotype-Tissue Expression project (GTEx v6, version phs000424.v6.p1, Bethesda, MD, USA) (https://gtexportal.org/home/testyourown) were used to perform expression quantitative trait loci analysis of 278 lung tissues. The expression levels LRBA in 57 pairs of lung adenocarcinoma samples versus their adjacent normal lung tissues were analyzed by The Cancer Genome Atlas (TCGA) database (collaborated between the NCI and the NHGRI, Bethesda, MD, USA) (https://cancergenome.nih.gov/).

2.5. Statistical Analysis

The Student’s t-test (for continuous variables) or the χ² test (for categorical variables) were used to examine the differences of the characteristics for CWP patients and control subjects. For the case–control study, Hardy–Weinberg equilibrium (HWE) was tested by using a goodness-of-fit χ²-test. The associations between polymorphisms in LRBA and risk of CWP were estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs) from unconditional logistic regression analysis with the adjustment for the possible confounders including age, dust-exposure years, smoking status, and job type. For the stratified analysis, the age and dust-exposure cut-offs used were according to the median age and dust-exposure years of the recruited patients and controls. The statistical power was calculated by the PS software (version 3.1.2, Vanderbilt University, Nashville, TN, USA) (http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize). All statistical tests were two-sided and p < 0.05 was considered a significant difference. All data arrangement and statistical analysis were performed with SPSS 13.0 software (Chicago, IL, USA).
3. Results

3.1. Characteristics of the Study Subjects

The demographic information of cases and controls enrolled in this study is summarized in Table 1. Mean age suggested no significance ($p = 0.086$) between CWP patients (67.3) and control group (66.3). Additionally, the exposure years ($p = 0.170$), smoking status ($p = 0.088$), and job type ($p = 0.703$) of CWP were similar to the controls. However, the pack-years smoked in CWP cases was significantly less than that of controls ($p < 0.001$). The frequency distributions and means of the selected characteristics were matched adequately between cases and controls. Furthermore, the cases of stages I to III were 431 (61.3%), 209 (19.7%), and 63 (9.0%), respectively.

| Table 1. Demographic and selected variables among the coal workers’ pneumoconiosis (CWP) cases and controls. |
| --- |
| **Variables** | **CWP ($n = 703$)** | **Controls ($n = 705$)** | **$p$** |
| Age, years (mean ± SD) | $67.3 ± 10.8$ | $66.3 ± 9.7$ | 0.086 |
| Exposure years (mean ± SD) | $24.9 ± 8.5$ | $25.5 ± 7.1$ | 0.170 |
| Smoking | | | 0.088 |
| No | 374 | 53.2 | 343 | 48.7 |
| Yes | 329 | 46.8 | 362 | 51.3 |
| Pack-years smoked | | | $<0.001$ |
| 0 | 374 | 53.2 | 343 | 48.7 |
| 0–20 | 201 | 28.6 | 165 | 23.4 |
| >20 | 128 | 18.2 | 197 | 27.9 |
| Job type | | | 0.703 |
| Tunnel and coal mining | 590 | 83.9 | 599 | 85.0 |
| Transport | 40 | 5.7 | 42 | 6.0 |
| Others | 73 | 10.4 | 64 | 9.1 |
| Stage | | | |
| I | 431 | 61.3 | | |
| II | 209 | 29.7 | | |
| III | 63 | 9.0 | | |

Data with $p < 0.05$ was in bold.

3.2. Associations between the LRBA Polymorphisms and Risk of CWP

In Table 2, we listed the primary information and frequencies of LRBA polymorphisms. All genotype distributions of control subjects were consistent with those expected from the HWE ($p > 0.05$). The MAF of all three selected SNPs was consistent with that reported in the HapMap database (http://www.hapmap.org). In addition, all three SNPs could lead to different transcription for located in the exon regions.

| Table 2. Primary information of genotyped SNPs in lipopolysaccharide (LPS)-responsive beige-like anchor protein (LRBA). |
| Cluster ID | Region | dbSNP Allele | Function | Protein Residue | MAF Case | MAF Control | HWE * |
| rs2290846 | Exon-56/57 | G > A | missense | Ser/Leu | 0.256 | 0.279 | 0.060 |
| rs3749574 | Exon-54/57 | C > T | missense | Ala/Thr | 0.251 | 0.275 | 0.504 |
| rs1782360 | Exon-54/57 | G > C | missense | Ala/Gly | 0.125 | 0.123 | 0.091 |

HWE * (Hardy–Weinberg equilibrium) $p$ value in the control group. MAF: minor allele frequency; SNP: single nucleotide polymorphism.
Next, a multivariate logistic regression analysis was performed to assess the effect of SNPs on CWP risk (adjusting for age, exposure years, pack-years smoked, and job type). As shown in Table 3, the parameters for the association of SNPs with CWP suggested that only LRBA rs2290846 significantly associated with the risk of CWP. No significant difference in two other LRBA SNPs (rs3749574 and rs1782360) was observed between CWP patients and healthy controls under any of the genetic models. The analysis under different genetic models revealed that the risk allele decreased the susceptibility to CWP under co-dominant (AA versus GG; OR = 0.64, 95% CI = 0.43–0.96, \( p = 0.030 \)), and the association remained significant after adjusting for age, exposure years, pack-years smoked, and job type. In addition, under the recessive model of LRBA rs2290846 (AA versus GG + GA; adjusted OR = 0.60, 95% CI = 0.40–0.89, \( p = 0.011 \)), significant distribution difference was found between CWP patients and controls.

### Table 3. Distributions of genotypes of LRBA and their associations with CWP risk.

| Variables | CWP Cases | Controls | OR (95% CI) \(^a\) | \( p \) \(^a\) | OR (95% CI) \(^b\) | \( p \) \(^b\) |
|-----------|-----------|----------|-------------------|----------|-------------------|----------|
|           | \( n = 695 \) | \( n = 684 \) | | | | |
| rs2290846 |           |          |                   | | | |
| GG        | 384       | 371      | 1.00              | -        | 1.05 (0.84–1.31) | 0.677 (0.84–1.32) | 0.680 |
| GA        | 266       | 245      | 1.05 (0.84–1.31) | 0.677    | 1.05 (0.84–1.32) | 0.680 |
| AA        | 45        | 68       | 0.64 (0.43–0.96) | 0.030    | 0.61 (0.41–0.92) | 0.018 |
| Dominant  | 0.96 (0.78–1.19) | 0.706 (0.57–1.18) | 0.658 |
| Recessive | 0.63 (0.42–0.93) | 0.020 | 0.60 (0.40–0.89) | 0.011 |
| Additive  | 0.90 (0.76–1.06) | 0.196 | 0.89 (0.75–1.05) | 0.152 |
| rs3749574 |           |          |                   | | | |
| CC        | 386       | 360      | 1.00              | -        | 1.00              | -        |
| CT        | 274       | 284      | 0.90 (0.72–1.12) | 0.346   | 0.90 (0.72–1.13) | 0.364 |
| TT        | 38        | 48       | 0.74 (0.47–1.16) | 0.186   | 0.70 (0.45–1.10) | 0.124 |
| Dominant  | 0.88 (0.71–1.08) | 0.221 | 0.88 (0.71–1.09) | 0.232 |
| Recessive | 0.77 (0.50–1.20) | 0.249 | 0.73 (0.47–1.14) | 0.162 |
| Additive  | 0.88 (0.74–1.05) | 0.146 | 0.87 (0.73–1.04) | 0.127 |
| rs1782360 |           |          |                   | | | |
| GG        | 539       | 534      | 1.00              | -        | 1.00              | -        |
| CG        | 139       | 135      | 1.02 (0.78–1.33) | 0.883   | 1.01 (0.77–1.32) | 0.943 |
| CC        | 17        | 24       | 0.99 (0.50–1.96) | 0.979   | 1.01 (0.51–2.02) | 0.971 |
| Dominant  | 1.02 (0.79–1.31) | 0.898 | 1.01 (0.78–1.30) | 0.964 |
| Recessive | 0.99 (0.50–1.95) | 0.969 | 1.01 (0.51–2.00) | 0.985 |
| Additive  | 1.01 (0.81–1.26) | 0.922 | 1.01 (0.81–1.25) | 0.964 |

Abbreviations: Dominant, wild homozygote versus heterozygote and mutational homozygote; Recessive, wild homozygote and heterozygote versus mutational homozygote; Additive, wild homozygote versus heterozygote versus mutational homozygote. \(^a\) Two-sided \( \chi^2 \) test. \(^b\) Adjusted for age, exposure years, pack-years smoked and job type in logistic regression model. Data with \( p < 0.05 \) was in bold.

In Table 4, stratification analysis according to exposure years and pack-years smoked was used to assess the associations between LRBA rs2290846 and CWP under a recessive model. Data suggested that in the subjects who had more than 27 years of exposure, the individuals of rs2290846 AA genotype had significantly decreased CWP risk compared with GG/GA genotypes (OR = 0.51, 95% CI = 0.28–0.94, \( p = 0.032 \)) (Table 4), while no significant difference was observed in the subjects with less than 27 years of exposure (\( p = 0.237 \)). This AA genotype also decreased CWP risk in the non-smoker population (OR = 0.58, 95% CI = 0.34–1.00, \( p = 0.049 \)). Further analysis between CWP stage and genotypes of rs2290846 also proved that the AA genotype of rs2290846 could function as protective factor—especially in total CWP (OR = 0.60, 95% CI = 0.40–0.89, \( p = 0.011 \)) and stage I patients (OR = 0.60, 95% CI = 0.37–0.97, \( p = 0.035 \)). Since the sample size is relatively small, the protective role was not significant in stages II and III groups (Table 5).
Table 4. Stratified analysis between the genotypes of LRBA rs2290846 and CWP risk.

| Variables                      | rs2290846 | Cases a | Controls a | OR (95% CI) b | p b  |
|--------------------------------|-----------|---------|------------|---------------|------|
| Exposure years                 |           |         |            |               |      |
| <27                            | 341/27    | 355/37  | 0.73 (0.43–1.23) | 0.237 |
| ≥27                            | 309/18    | 261/31  | 0.51 (0.28–0.94) | 0.032 |
| Pack-years smoked              |           |         |            |               |      |
| 0                              | 343/24    | 302/36  | 0.58 (0.34–1.00) | 0.049 |
| >0–20                          | 184/16    | 138/19  | 0.65 (0.32–1.33) | 0.241 |
| >20                            | 123/5     | 176/13  | 0.57 (0.20–1.69) | 0.313 |

a Heterozygote+Wild type homozygote/Variant homozygote; b Adjusted for age, exposure years, pack-years smoked, and job type. Data with p < 0.05 was in bold.

Table 5. Stratified analysis between the genotypes of LRBA rs2290846 and CWP stage.

| Variables | Cases/Controls | Genotypes (Cases/Controls) | p a  | OR (95% CI) a |
|-----------|----------------|----------------------------|------|---------------|
|           |                | AA            | GG/GA | N       | %         | N       | %         | N       | %         |       |          |      |          |
| Total     | 703/705        | 45/68         | 6.4/9.6 | 658/637 | 93.6/90.4 | 0.011   | 0.60 (0.40–0.89) |
| Stage     |                |               |        |         |           |         |           |         |           |      |          |      |          |
| I         | 431/705        | 26/68         | 6.0/9.6 | 405/637 | 94.0/90.4 | 0.035   | 0.60 (0.37–0.97) |
| II        | 209/705        | 14/68         | 6.7/9.6 | 195/637 | 93.3/90.4 | 0.137   | 0.62 (0.34–1.16) |
| III       | 63/705         | 5/68          | 7.9/9.6 | 58/637  | 92.1/90.4 | 0.381   | 0.65 (0.24–1.72) |

a Adjusted for age, exposure years, pack-years smoked, and job type in logistic regression model.

3.3. Potential Biological Roles of LRBA rs2290846 in CWP

Since rs2290846 is located in the exon area of LRBA and has the potential ability to influence LRBA protein, we investigated the potential biological function of rs2290846 G > A polymorphism. HaploReg v4.1 was used to develop the potential mechanism of the rs2290846 variant on clinical phenotypes and normal variation by searching SNPs with high LD (Supplementary Table S1). To further testify the function of rs2290846, the expression quantitative trait loci (eQTL) was performed by using GTEx Analysis Release V6p (https://gtexportal.org/home/testyourown). The results showed that in the normal lung tissues, the AA genotype of SNP rs2290846 is associated with decreased LRBA expression, although the significance is limited (p = 0.057) (Figure 1). By using the TCGA database, we analyzed the expression levels of LRBA in 57 lung adenocarcinoma samples and paired adjacent normal lung tissues. The data suggest relatively higher expression of LRBA in lung cancer tissues (*** p < 0.001) (Figure S1). These results hinted at a potential protective role of rs2290846 in pulmonary fibrosis.
4. Discussion

In the present study, we investigated the potential association between LRBA polymorphisms and risk of CWP in a Chinese population. Our results found that LRBA rs2290846 G > A—which is located in the exon area of LRBA—closely associated with CWP. The phenomenon was significantly observed especially in non-smokers and individuals with longer exposed years. TCGA and eQTL analysis further supported the protective role of the rs2290846 AA genotype by decreasing the level of LRBA protein.

Coal is the major energy source in China [25]. Meanwhile, the occupational disease CWP is usually accompanied with systematic autoimmune diseases. LRBA serves as a key regulator in T-cell function, and mutation in LRBA could cause T-cell deficiency and immune dysregulation [21]. However, the germline mutation of LRBA has not yet been studied. Recently, the roles of autophagy have been recognized in a variety of diseases. In pulmonary fibrosis, autophagy has been considered as a “cleaner”, and serves to degrade matrix molecules including fibronectin and collagen before they are secreted. Research has proved that autophagy is involved in pulmonary fibrosis and acts as a key point during this process. Meredith et al. considered autophagy as a protective mechanism against pulmonary fibrosis by its effect on myofibroblast differentiation [26], and one of our former studies also supported its protective role [19]. Meanwhile, deficient LRBA has been found to reduce autophagy through lysosome functions [27]. It is quite clear that autophagosomal–lysosomal fusion is one of the most important processes during autophagy. As there are homologs of LRBA and lysosomal functions, mice with mutations in lysosomal proteins have similar phenotypes to those with mutations in the autophagic pathway [27,28]. Taken together, it is reasonable to presume that genetic variations in LRBA may affect autophagy in CWP.

In this study, we revealed LRBA gene polymorphisms may have potential influence on the risk of CWP in a Chinese population. Of note, we have identified a significant association with CWP risk at rs2290846 located at 4q31.3, which is the 56th exon region of LRBA. This G > A mutation is a missense mutation, converting the serine to leucine, which might influence the expression of LRBA and affect its function. The protective role of rs2290846 AA was further proposed by stratified analysis, but the small sample size of cases in stage II and III restricted our conclusion. By using eQTL, we found that the AA genotype of SNP rs2290846 was associated with a decreased LRBA expression in normal...
lung. Due to the limited sample size, the \( p \)-value is not significant, and a larger cohort may better reveal its regulatory role. To further explore the role LRBA played in diseases, we used TCGA lung adenocarcinoma tissues to validate its expression. The results suggested a higher level of LRBA in the pathological tissues, which also supported that rs2290846 may decrease disease occurrence by regulating LRBA expression. Our previous study also suggested that polymorphisms in another autoimmune-related gene (GIRT) are strongly associated with CWP [29], which reminds us of the importance of autoimmunity in the process of pulmonary fibrosis. More evidence is needed to verify the role LRBA played during pulmonary fibrosis, and perhaps further findings focused on the tissues of pulmonary fibrosis could shed new light on the therapeutic targets in CWP. To our best knowledge, this is the first research focused on LRBA polymorphisms.

We found that a protective effect of the rs2290846 AA genotype were evident compared with GG/GA. Though the specific underlying mechanisms are not clear, considering LRBA function in autoimmune and autophagy, we still could make a putative educt. Chen et al. suggested that decreased lysosome numbers lead to the increased formation of autophagosomes, exacerbating the apoptosis in alveolar macrophages of silicosis, preventing autophagosomes from benefitting silicosis [18]. It has also been proved that LRBA deficiency could reduce autophagy level in B cells [27]. We proposed that the rs2290846 AA genotype may play an important role in decreased levels of LRBA, which is related to autophagy and reduced risk of CWP. Interestingly, there was no significant difference between smokers and non-smokers related to CWP risk (\( p = 0.088 \)), but a former study showed that smoking was significantly associated with silicosis [30]; this may due to insufficient sample size. In the present study, we also found that the LRBA rs2290846 variant played a more obvious protective role in nonsmokers with long dust exposure history and stage I CWP. It is possible that cigarette smoke and dust exposure blur the protective role of rs2290846 in CWP risk.

Though we have analyzed the relationship between LRBA SNPs and CWP risk, several limitations of our study still exist. First of all, our subjects are coal miners in China, which may cause selection bias. Secondly, more biological background data and functional studies in CWP patients would be quite helpful to explain the correlation between rs2290846 and CWP risk. Furthermore, other environmental exposure or factors (e.g., dietary habits) may be closely associated with LRBA, except for cigarette smoke and occupational exposure. Further genome-wide association study with a larger population and relevant molecular mechanism study could help us to improve our understanding about LRBA SNPs in CWP.

5. Conclusions

The present study first suggests that LRBA rs2290846 polymorphism is associated with CWP susceptibility in a Chinese population. It is also suggested that LRBA might be a potential diagnostic biomarker for CWP. Further studies focused on detailed mechanism or with larger cohorts are warranted to validate our findings.

Supplementary Materials: The following are available online at www.mdpi.com/1660-4601/14/10/1138/s1. Table S1: High LD SNPs related to rs2290846. Figure S1. The LRBA expression level in lung adenocarcinoma (\( n = 57 \)) and paired adjacent normal lung tissues (\( n = 57 \)). The primary LRBA expression data in lung adenocarcinoma patients were downloaded from the TCGA database (*** \( p < 0.001 \)).

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