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Chronic Obstructive Pulmonary Disease Susceptibility and the Surfactant Protein B Gene

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ABSTRACT

Background: Chronic obstructive pulmonary disease susceptibility is known to be significantly influenced by genetic predisposition in addition to smoking (COPD). For COPD, a number of potential genes have been suggested, including surfactant protein B. (SFTPB). To clarify the role of SFTPB in COPD, however, comprehensive investigations in populations with various ethnic backgrounds and circumstances are needed.

Aims & Objective : In a population, we looked into the relationship between SFTPB polymorphisms and lung function susceptibility to COPD.

Methods & Materials : The SFTPB gene's four single nucleotide polymorphisms (SNPs) were genotyped in 480 COPD patients and 487 healthy individuals. Comparing genotype and allele frequencies between patients and controls allowed researchers to look into any possible connections between these SNPs and lung function. Additionally, associations between COPD susceptibility and haplotypes were evaluated.

Results: The SFTPB exon polymorphism rs1130866 significantly reduced the risk of COPD in individuals (adjusted P = 0.003) and was linked to a rise in forced expiratory volume in one second (FEV1) (adjusted P=0.012).

Conclusions: In the population, SFTPB polymorphisms are related to COPD risk and lung function.

Keywords: genetics; single nucleotide polymorphisms; spirometric phenotypes

1. INTRODUCTION

The fourth largest cause of death worldwide, CHRONIC obstructive pulmonary disease (COPD) is a key contributor to chronic morbidity and mortality[1]. [2] Although genetic variations also have a role in the susceptibility to the disease, COPD is a complex condition brought on by environmental variables such as tobacco use and air pollution from burning biomass in underdeveloped areas[3-5]. Alpha-1 antitrypsin, matrix metalloproteinase 127, and the SERPINE2 gene are only a few of the candidate genes that may be linked to the emergence of COPD. [8] The gene for surfactant protein B (SFTPB), one of the most significant genes associated with COPD susceptibility, has been studied in a variety of ethnic

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groups. The family of surfactant proteins includes the protein SFTPB. The surfactant layer, which is made up of surfactant proteins, is crucial for the stability of the bronchioles, immunological defence, and control of inflammatory reactions in the lung. [9] SFTPB, together with other proteins and phospholipids, creates a barrier on the surface of the alveoli that prevents damage to the alveoli during breathing and is largely generated and secreted by type II cells[10].

The SFTPB gene has been linked to pulmonary illnesses and lung function in earlier research. [11,12] When SFTPB is severely deficient, it can result in the deadly respiratory distress syndrome that affects newborns13, although moderate deficiency has been linked to decreased lung function and an increased risk of COPD when combined with other risk factors. [14,15] Due to SFTPB's crucial role, the associations between SFTPB polymorphisms and COPD susceptibility or lung function have been examined in a number of populations; however, no significant study has been carried out in a population to yet. Therefore, we proposed that genetic variations of the SFTPB gene may be linked to decreased lung function and may affect the onset of COPD in people. We genotyped 1372 adult people in southwestern to test this hypothesis and then examined the relationships between SFTPB SNPs and risk of COPD and lung function.

2. MATERIALS AND METHODS

An epidemiological survey of adults aged 560 was carried out. According to the inclusion criteria for cases, 480 of the 5760 unrelated Han people who were randomly chosen and who underwent a questionnaire, physical exam, and pulmonary function testing had been diagnosed with COPD. The remaining 487 control subjects were drawn from the non-COPD population and were matched for age, sex, and smoking history. All subjects gave their written consent after being fully informed. The Hospital at Santosh University, located in Ghaziabad, granted ethical approval. Patient recruitment and clinical evaluations were done in accordance with GOLD standards, which stands for the Global Initiative for Chronic Obstructive Lung Disease. [1]

Age 740 years, chronic airway symptoms including dyspnea, chronic coughing, or sputum production, and the presence of persistent airflow limitation (post-bronchodilator forced expiratory volume in 1 second [FEV1]/forced vital capacity [FVC],0.7) were the inclusion criteria for COPD patients. The inclusion criteria for control subjects were normal spirometry (FEV1 7 80% and FEV1/FVC. 0.7) and age of 740 years.

All individuals had to have no history of autoimmune disorders, bronchial asthma, lung cancer, or a recent respiratory infection in order to be excluded from the study. A family history of COPD was another exclusion factor for controls. Age, sex, body mass index (BMI), and pack-years of smoking were all used to try and match cases and controls. selection of single nucleotide polymorphisms. We genotyped four SFTPB single nucleotide polymorphisms (SNPs) (rs2118177, rs2304566, rs1130866 and rs3024791). These SNPs were chosen based on previous research showing strong relationships with COPD risk and associated symptoms. [11,16,17] Table 1 lists the fundamental traits of the patient.

Genotyping

Using a commercially available extraction kit (Tiangen Biotech, Beijing, China), genomic DNA was isolated from peripheral blood in accordance with the manufacturer's instructions. The Beijing Genomics Institute (BGI; Shenzhen, China) genotyped each individual using Sequenom's Mass ARRAY mass spectrometer-compatible iPLEX SNP genotyping procedure

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(Sequenom, San Diego, CA, USA). 18 About 5% of samples were genotyped twice for quality control to ensure concordance; no differences were found in the repeat testing. Additionally, a number of samples were additionally genotyped using restriction enzyme digestion to validate the BGI genotyping results. The outcomes agreed completely. The case or control status of the samples had no bearing on the genotyping process.

Statistical analysis

The SPSS 18.0 software suite was used to conduct the statistical analysis (Statistical Package for the Social Sciences, Chicago, IL, USA). Data are shown as a mean with a 6 standard deviation range. Using the Student's t-test, the mean values of continuous variables were compared. For each case and control, the genotype and allele frequencies were determined by direct counting. The genotype and allele distributions between patients and controls were compared using v2 tests. By using logistic regression and controlling for age, sex, BMI, and pack-years of smoking, associations between each SNP and risk of COPD were examined. Individual SNP allele distributions relative to the common allele and genotype distributions relative to the predominant homozygous genotype were computed, along with odds ratios (ORs) and 95% confidence intervals (CIs). Additionally, using linear regression and adjusting for the aforementioned potential confounders, the associations between SNPs and lung function were examined. Haplotype analysis was undertaken using Haploview 4.2 software (MIT/Harvard Broad Institute, Cambridge, MA, USA; http://www. broad. mit.edu/mpg/haploview). A goodness-of-fit v2 test was used to determine whether each SNP deviates from Hardy-Weinberg Equilibrium (HWE) in controls. P 0.05 was used as the threshold for significance.

Table 1: Polymorphisms in the SFTPB gene in this study

SNP No	SNP name	Public location position	Function	Allele(major/minor)
1	*rs*2118177	85743804	Intron	T/ C
2	*rs*2304566	85744269	Intron	A/ G
3	*rs*1130866	85747252	Exon	C/ T
4	*rs*3024791	85749215	Promoter region	G/ A

Table 2: Clinical features of COPD patients and controls

Parameter	COPD (n =480)	Controls (n=487)	P-value
	Mean±S.D.	Mean±S.D.	
Male, *n* (%)	273 (71.0)	266 (69.3)	0.481*
BMI, kg/m^2, *n* (%)	21.34 (3.49)	21.43 (3.32)	0.085†
Age, years			
＜45	41.74 ± 1.95	41.64 ± 1.89	0.663
45–60	55.47 ± 3.77	54.83 ± 3.96	0.118
＞60	67.34 ± 5.81	69.62 ± 5.82	0.589

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Smoking history Never-smoker, *n* (%)	159 (33.1)	164 (33.6)	0.831
Ever-smokers, *n* (%)‡	321 (66.9)	323(66.4)	
Pack-years for ever smokers§	32.76 ± 20.68	28.19±21.33	0.002
ulmonary function tests Predicted FEV_1 %	63.27 ± 24.92	103.36 ± 15.54	≺0.001
Predicted FVC %	98.30 ± 41.45	106.26± 17.81	0.015
FEV_1/FVC	55.38 ± 12.46	78.27 ± 6.13	≺0.00

3. RESULTS

Table 2 provides a summary of the study population's clinical characteristics. There were no appreciable variations in terms of sex, age, BMI, or smoking habits. Differences between pack-years for smokers who had never smoked before were seen in two groups (P 14 0.001). As anticipated, lung function was markedly worsened in COPD patients. It is important to note that there were no appreciable differences between cases and controls in the proportion of participants with a history of exposure to noxious particles or gases (data not shown). SFTPB polymorphism genotype and allele distributions and correlations with COPD We evaluated four SFTPB SNPs in 680 COPD patients and 687 controls to look for correlations between SFTPB and COPD. By case-control status, the genotype and allele frequencies are shown in Table.

The controls showed no variation from HWE. In the unadjusted analysis, the SFTPB exon polymorphism rs1130866 significantly reduced the risk of COPD in individuals (P = 0.024); the significance was further strengthened when the significance was corrected for clinical confounders like age, sex, BMI, and pack-years of smoking (P = 0.004). In COPD patients, the genotype frequencies of CC, CT, and TT were 0.546, 0.400, and 0.054 respectively, compared to 0.504, 0.406, and 0.090 in controls. The TT genotype may shield individuals against the condition, according to an analysis of the relationships between genotypes and COPD (OR 0.474, 95%CI 0.301-0.746). Even after modifying the model for age, sex, BMI, and pack-years in logistic regression, there were no relationships between the other SNPs evaluated (rs2118177, rs2304566, and rs3024791) with COPD. The frequency of the T allele of SNP rs1130866 was substantially lower in COPD patients than in controls (0.254 vs. 0.293, P=0.023), and the significance increased after adjusting for age, sex, BMI, and pack-years (P =0.006). This finding is consistent with the genotyping analysis. The T allele was linked to a lower likelihood of developing COPD (OR 0.784, 95%CI 0.661-0.930).

However, neither before nor after controlling for pertinent clinical variables, there were no appreciable variations in the allele frequencies of the remaining SNPs (rs2118177, rs2304566, and rs3024791). pulmonary function phenotype association analysis After controlling for age, sex, BMI, and pack-years of smoking, stepwise linear regression analysis in all subjects revealed that the TT genotype in rs1130866 is associated with an increase in predicted FEV1 (b 14 0.067, P 14 0.014) (Figure 1), but the association between rs1130866 and FEV1/FVC was not discovered. The three SNPs (rs2118177, rs2304566, and rs3024791) that were evaluated did not correlate with pulmonary function (Table 4). Analyses of haplotypes D0 and r2 were used to determine pairwise linkage disequilibrium for the four SFTPB SNPs based on the genotyping data analysed with Haploview 4.2. (Figure). Block 1 on the LD map contained two SNPs (rs2118177 and rs2304566) that were in strong linkage

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disequilibrium (LD) and displayed three distinct haplotypes (TA, CA, and CG) there. The other SNPs showed typically low LD, and the r2 between rs2304566 and rs3024791 was 0.523. We also evaluated the connections between COPD and haplotypes. The distribution of any haplotype did not significantly differ between COPD patients and controls, though (Appendix Table A*).

4. DISCUSSION

We examined into possible correlations between four SFTPB SNPs and the onset of COPD and lung function in this case-control study. We demonstrated that the exon polymorphism of the SFTPB gene, Tallele of rs1130866, protected Chinese Han participants from COPD. Additionally, we showed that rs1130866 was connected to a higher projected FEV1%. However, neither COPD nor lung function were associated with the other three SNPs, which included the promoter variant rs3024791 and two intron variants rs2118177 and rs2304566. Numerous analyses of the relationships between SFTPB and the onset of COPD and lung function in various groups have been conducted, however the outcomes have been mixed. Hersh et al. examined SFTPB variations in a US population and discovered a connection between the Thr131Ile or rs1130866 SNP with moderate-to-severe airway obstruction (P = 0.03) in a family-based analysis, which is in keeping with our findings. [19] Similar to this, Guo et al. examined the associations between SFTPB polymorphisms and COPD susceptibility in Mexicans, and after controlling for sex, age, and smoking, discovered a significant link between B1580 C (rs1130866) and COPD (OR 3.39, P = 0.02) compared with smoker controls. [11]

In the study by Bækvad-Hansen et al., there was no significant association between the SFTPB promoter polymorphism rs3024791 and lung function and COPD in a Danish population.[19

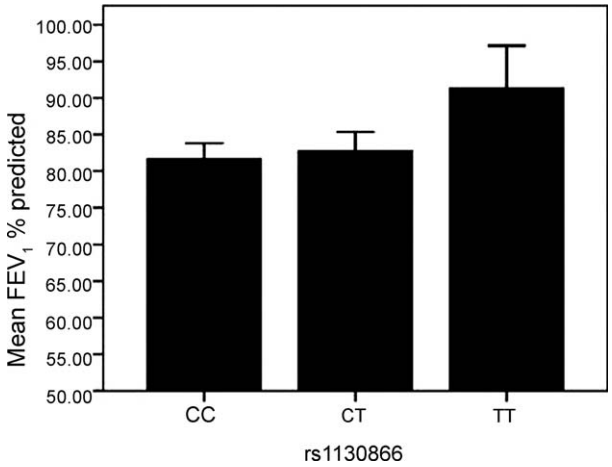

Figure 1: The association between rs1130866 and FEV1% predicted in all subjects. Data represent mean 6 standard error. The model was adjusted by age, sex, BMI and pack-years of smoking. FEV1 ¼ forced expiratory volume in 1 s; BMI ¼ body mass index.

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A study in Central China found that the SP-B 1580 (rs1130866) T allele was probably linked to higher susceptibility to COPD, which is in contradiction to our findings. Ezzeldin et al. found that the T allele of rs1130866 was connected with COPD risk (P= 0.005) and impairment of pulmonary function. [21] Additionally, Thomas et al. came to the conclusion that the rs3024791 SNP decreased SFTPB transcription in H441 cells. [22] We could not discover any correlation between this SNP and the onset of COPD or lung function, though. The aggravated phenotype of COPD was substantially related with haplotypes with three or four loci (rs2304566-rs1130866-rs3024791) or with four loci (rs2304566-rs1130866-rs2077079-rs3024791) in a multicenter, randomised clinical trial, but no such association was observed in the current investigation. [16] There may be a number of explanations for the apparent variances between the findings of different studies, including demographic stratification, genetic variability, phenotypic heterogeneity, and variations in study techniques and/or sample sizes. These differences are typically attributed to genetic variability. 19 On chromosome 2p12-p11.2, the human SFTPB locus may be found. It encodes the SFTPB protein, which is mostly released by type II alveolar epithelial cells. 10,23 The pulmonary surfactant (PS), which is made up of the mature protein and phospholipids, has a low molecular mass of 18 kDa and is hydrophobic.[24] Surface tension is decreased by the PS, which forms the air/liquid contact and covers the entire alveolar surface. In order to promote the creation and stability of the surfactant monolayer, 25 SFTPB increases the rate, adsorption, and distribution of phospholipids throughout the breathing cycle. 24 The regular operation of the PS and the normal function of the lungs depend on SFTPB. 26 An link between SFTPB and COPD susceptibility seems highly likely because lung function determines whether COPD is present and how severe it is. In this work, we established a link between the SFTPB SNP rs1130866 and lung function in a Chinese Han population. The amino acid 131 in SFTPB exon 4 is changed from threonine to isoleucine by the C-T substitution, potentially preventing N-linked glycosylation sites (Asn129–Gln–Thr131).[27] According to Wang et al., a protein with the T allele was not glycosylated at Asn129-Gln-Thr131 in a stable transfectant in vitro. [28] The folding and transport of the SFTPB protein through the endoplasmic reticulum to the Golgi may be significantly influenced by N-linked glycosylation, which may also have an impact on co- or post-translational protein modification and protein function. [29] In SFTPB, which contained the N-linked glycosylation recognition site of the N-terminal segment, Floros et al. showed that a C allele at the SNP 1580 (rs1130866) (C/T) site enhanced the risk of COPD. [14] A T allele at the same SNP, which lacked the aforementioned location, was, nevertheless, a preventative measure against various pulmonary illnesses, including respiratory distress syndrome. [30] Additionally, the T allele results in the replacement of isoleucine for threonine, which has been shown to influence pulmonary function and change the glysosylation state of the pro-SFTPB peptide. 31 It has been shown that the usage of modified SFTPB sequences cloned into an expression system, where residue 131 is in a section of the propeptide, is essential and sufficient for intracellular trafficking of the mature peptide, however the biological effects of this in humans are not yet entirely obvious. [32] Therefore, the absence of Nlinked glycosylation sites, which may also alter the predicted FEV1%, may be associated to the protective effect of the Tallele at rs1130866 in the SFTPB gene against COPD in the Chinese Han population. The molecular aetiology of these effects is still unknown, though. unclear.

There are also some potential drawbacks to our study. The population analysed here may not be entirely typical of all of China's population because all of the individuals were only enrolled in the southwest, therefore our study's findings should be taken cautiously in

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populations from other regions of China. Second, there were 12 researchers involved in this very large epidemiological study, which used two pulmonary function test machines to analyse each participant's lung function. Therefore, any variation in the technical tests could lead to inaccurate data and random noise. Third, failure to account for multiple testing could result in false-positive results in any complex disease genetics study that involves several statistical comparisons.However, as the optimal method for adjusting for multiple testing is not clear, no adjustment was made in this study.

5. CONCLUSION

It came to the conclusion that the study's findings supported the hypothesis that SFTPB polymorphisms are related to COPD and lung function in a Chinese Han population. We may be able to better grasp the pathophysiology of COPD with the use of this information. To fully understand the impact of genetic factors on the specific pathophysiology of COPD, more research is required.

Acknowledgements:
Conflict of interest:

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