Original Article

Associations of Polymorphism of rs9944155, rs1051052, and rs1243166 Locus Allele in Alpha-1-antitrypsin with Chronic Obstructive Pulmonary Disease in Uygur Population of Kashgar Region

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Abstract

Background: Previous studies conducted in various geographical and ethnical populations have shown that Alpha-1-antitrypsin (*Alpha-1-AT*) expression affects the occurrence and progression of chronic obstructive pulmonary disease (COPD). We aimed to explore the associations of rs9944155AG, rs1051052AG, and rs1243166AG polymorphisms in the *Alpha-1-AT* gene with the risk of COPD in Uygur population in the Kashgar region.

Methods: From March 2013 to December 2015, a total of 225 Uygur COPD patients and 198 healthy people were recruited as cases and controls, respectively, in Kashgar region. DNA was extracted according to the protocol of the DNA genome kit, and Sequenom MassARRAY single-nucleotide polymorphism technology was used for genotype determination. Serum concentration of Alpha-1-AT was detected by enzyme-linked immunosorbent assay. A logistic regression model was used to estimate the associations of polymorphisms with COPD.

Results: The rs1243166-G allele was associated with a higher risk of COPD (odds ratio [*OR*] = 2.039, 95% confidence interval [*CI*]: 1.116–3.725, $P = 0.019$). In cases, *Alpha-1-AT* levels were the highest among participants carrying rs1243166 AG genotype, followed by AA and GG genotype ($\chi^2 = 11.89$, $P = 0.003$). Similarly, the rs1051052-G allele was associated with a higher risk of COPD (*OR* = 19.433, 95% *CI*: 8.783–43.00, $P < 0.001$). The highest *Alpha-1-AT* levels were observed in cases carrying rs1051052 AA genotype, followed by cases with AG and GG genotypes ($\chi^2 = 122.45$, $P < 0.001$). However, individuals with rs9944155-G allele exhibited a lower risk of COPD than those carrying the rs9944155-A allele (*OR* = 0.121, 95% *CI*: 0.070–0.209, $P < 0.001$). In both cases and controls, no significant difference in *Alpha-1-AT* levels was observed among various rs9944115 genotypes.

Conclusions: rs1243166, rs9944155, and rs1051052 sites of *Alpha-1-AT* may be associated with the COPD morbidity in Uygur population. While rs1243166-G allele and rs1051052-G allele are associated with an increased risk of developing COPD, rs9944155-G allele is a protect locus in Uygur population. *Alpha-1-AT* levels in Uygur COPD patients were lower than those in healthy people and differed among patients with different rs1051052 AG and rs1243166 AG genotypes.

Key words: Alpha-1-antitrypsin; Chronic Obstructive Pulmonary Disease; Polymorphism; Uygur Population

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation and is a preventable and treatable disease. COPD is associated with enhanced inflammatory response in the airways and lung to the noxious particles and gasses. Currently, COPD is the fourth leading cause of death globally and is a major cause of morbidity.[1] It predicts that COPD will become the third leading cause of death worldwide by 2030.[2] The

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aging population worldwide and the ongoing exposure to risk factors are expected to further increase the prevalence of COPD.[3]

The development of COPD is affected by many factors. In addition to environmental factors like air pollution, evidence has shown that genetic factors might also be involved in the pathogenesis of COPD.[4] *Alpha-1-AT*, also known as esterase inhibitor-1 gene (protease inhibitor 1 [PI]), is localized on 14q32 and encodes serine PIs. The inhibition of the proteolytic activity protects the lung.[5] Several studies reported that the Alpha-1-antitrypsin (*Alpha-1-AT*) deficiency was significantly associated with the incidence of pulmonary emphysema.[6] In addition, one study estimated that about 1–2% of COPD might be caused by genetic deficiency in *Alpha-1-AT*.[7] However, the evidence is limited, as only a few epidemiological studies have explored the relationship between *Alpha-1-AT* gene polymorphism and COPD. One study showed that patients with PiSZ genotype may increase the risk of COPD, but the *Alpha-1-AT* PiSS genotype was not significantly associated with COPD risk.[8] Therefore, it is unclear whether other loci of the *Alpha-1-AT* gene affect the development of COPD. To fill this gap, we performed a case-control study in Uygur population in the Kashgar region, to investigate the possible relationship between the polymorphism of the rs1243166, rs9944155, and rs1051052 site of the *Alpha-1-AT* gene and COPD.

Methods

Ethical approval

The study was approved by the Medical Ethics Review Committee of the First People's Hospital in Kashgar. Informed consents were obtained from all participants in this study.

Study population

All subjects were enrolled from the First People's Hospital in Kashgar, from March 2013 to December 2015. The study selected 225 Uygur COPD patients as the case group who fulfilled the following criteria: (1) the COPD diagnosis was according to the Global Initiative for Obstructive Lung Disease guidelines;[9] (2) COPD is diagnosed by typical history, clinical manifestations, and chest X-ray or computed tomography (CT); (3) the index of pulmonary function, an indication of chronic airway obstruction, was defined as a forced expiratory volume in 1 (FEV1)/forced vital capacity (FVC) <70% after inhalation of 400 μg salbutamol; (4) the patients can be checked only after ceasing the usage of the drug including the controlled release theophylline tablets for 24 h, β2 receptor agonist for 12 h, and inhaled β2-agonist and anticholinergic drugs for 4 h. According to the principle of group matching (age and gender), 198 Uygur healthy individuals constituted the control group, satisfying the following conditions: (1) the individuals did not present chronic bronchitis and emphysema in chest X-ray or chest CT; (2) the normal lung function was described as FEV1% >80% and an FEV1/FVC >70% after inhalation of 400 μg salbutamol; (3) the individuals had no diseases such as bronchiectasis, tuberculosis, interstitial disease, asthma, and cancers. All the participants were of Uygur ethnicity and shared no kinship with each other. Information on gender, age, smoking status, and lung function was collected by questionnaire.

SequenomMassARRAY single-nucleotide polymorphism testing

DNA extraction

We collected 2 ml venous blood from all the participants. DNA extraction from blood samples was performed with Greiner Genomic DNA purification Kit (Greiner, Germany). DNA samples with adjusted concentration of 50 ng/μl were stored at −80°C storage box (DW-86L728; Qingdao Haier, China).

Primer design

Genotyping was performed by polymerase chain reaction (PCR). The following primers (Shanghai YingJun Biotechnology Co., China) were used for PCR amplification: rs1243166: PCR primers: 2nd-PCRP: 5'-ACGTTGGATAAAGCACATCACCCATTGACC-3'; 1st-PCRP: 5'-ACGTTGGATGAAGAAGTCAGGCTGCATGTG-3'; UEP_SEQ: 5'-CCCTCCCTTTCCTCC-3'. rs9944155: PCR primers: 2nd-PCRP: 5'-ACGTTGGATGAAAAGTTTGGGGACTGCTGG-3'; 1st-PCRP: 5'-ACGTTGGATGCAGAAATCACTGCTTAGCCC-3'; UEP_SEQ: 5'-CGGTGACTGCTGGCTTACAC-3'. rs1051052: PCR primers: 2nd-PCRP: 5'-ACGTTGGATGAGACCATTACCCTATATCCC-3'; 1st-PCRP: 5'-ACGTTGGATGCTGAGGAGTCCTTGCAATGG-3'; UEP_SEQ: 5'-GGATCCCTTCTCCTCCC-3'.

Single-nucleotide polymorphism genotyping

Multiplex PCR technique was used to amplify the gene sequences of the selected sites under the following conditions: initial denaturation at 94°C for 4 min, 45 cycles of 94°C for 20 s, 56°C for 30 s, 72°C for 1 min, and a final extension at 72°C for 3 min. The amplified products were purified by shrimp alkaline phosphatase and added to dNTP; the amplification of the single-nucleotide polymorphism (SNP) site was performed by a single base extension primer (about 20 bp). After extension, the DNA products purified with resins were detected by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MS) and SNP genotyping.[10]

Enzyme level detection

Five milliliters fasting venous blood was collected, laid up for 2 h with room temperature, and centrifuged at 626 × *g* for 5 min, with the serum being separated and stored at −20°C. The level of Alpha-1-AT in serum was detected by enzyme-linked immunosorbent assay.

Statistical analysis

The SPSS 18.0 (version 18.0, SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Numerical data were expressed as a mean ± standard deviation (SD). Deviations

from Hardy-Weinberg equilibrium (HWE) were evaluated using Chi-square test, and a value of $P > 0.05$ was considered as conforming the HWE. The difference between COPD patients and controls were also compared by Chi-square test. Univariate logistic regression model was applied to explore the relationship between COPD and the SNPs. The *Alpha-1-AT* levels between case group and control group and among different genotypes were compared by Wilcoxon rank-sum test. A $P < 0.05$ indicated a significant difference.

Results

Baseline characteristics of the study participants

A total of 423 Uygur individuals from Xinjiang Uygur Autonomous Region were enrolled in the study. Among them, 225 comprised the COPD group and 198 formed the control group. No significant differences were observed between the two groups with respect to gender, age, weight, body mass index, cigarette smoking, passive smoking, biofuel exposure, and animal dust exposure (all $P > 0.05$), but significant difference was found for occupational dust exposure ($\chi^2 = 4.694$, $P = 0.030$; Table 1).

Allelic and genotypic frequencies

The distributions of rs1243166, rs9944155, and rs1051052 genotype among the case and control group are shown in Table 2. The genotype distribution of *Alpha-1-AT* SNPs rs1243166 was in line with HWE in both case ($\chi^2 = 4.092$, $P = 0.129$) and control ($\chi^2 = 2.914$, $P = 0.233$) groups. For SNPs rs9944155 and rs1051052, genotype distribution was in line with HWE in the control group ($\chi^2 = 3.402$, $P = 0.183$), while they were not in the case group ($\chi^2 = 10.587$, $P = 0.005$). For rs1243166, the frequency of the AA genotype was 10.2% and 18.2% in the COPD and control group, respectively. The frequency of the GG/GA genotype was 89.8% and 81.8% in the case and control group, respectively. The frequencies of A and G allele were 33.1% and 66.9% in the case group and 39.9% and 60.1% in the control group, respectively. Significant differences were observed in the genotype ($\chi^2 = 5.559$, $P = 0.018$) and allele ($\chi^2 = 4.198$, $P = 0.040$) distribution between the case and control group. For rs9944155, the frequency of the AA genotype was 50.2% and 18.2% in the case and control group, respectively. The frequency of the GG/GA genotype was 49.8% and 81.8% in the case and control group, respectively. The frequencies of A and G allele were 67.8% and 32.2% in the case group and 37.1% and 31.9% in the control group. Significant differences were observed in the genotype ($\chi^2 = 47.386$, $P < 0.001$) and allele ($\chi^2 = 79.559$, $P < 0.001$) distribution between the case and control group. For rs1051052, the frequency of the AA genotype was 25.8% and 64.1% in the case and control group, respectively. The frequency of the GG/GA genotype was 74.2% and 35.9% in the case and control group, respectively. The frequencies of A and G allele were 47.1% and 52.9% in the case group and 80.1% and 19.9% in the controls. Significant differences were observed in the genotype ($\chi^2 = 62.991$, $P < 0.001$) and allele ($\chi^2 = 97.543$, $P < 0.001$) distribution between the case and control group [Table 2].

Association of single-nucleotide polymorphism with chronic obstructive pulmonary disease

Table 3 shows the association of rs1243166, rs9944155, and rs1051052 genotypes with COPD using logistic regression model. The risk of COPD in individuals carrying the rs1243166-GG and rs1243166-GA genotypes was 2.039-fold (95% confidence interval [*CI*]: 1.116–3.725; $P = 0.019$) and 1.875-fold (95% *CI*: 1.033–3.404, $P = 0.037$) than that of the rs1243166-AA genotype. In addition, we observed that the rs1051052-G allele posed a higher risk of COPD than that of the rs1051052-A allele (odds ratio [*OR*]: 19.433, 95% *CI*: 8.783–43.00, $P < 0.001$). However, individuals carrying the rs9944155-G allele had a lower risk of COPD than those carrying the rs9944155-A allele (*OR*: 0.121, 95% *CI*: 0.070–0.209, $P < 0.001$).

Associations of Alpha-1-antitrypsin levels with genotype

Alpha-1-AT levels in control group were significantly higher than those in COPD group ($Z = 3.4820$, $P < 0.0001$). We further compared the *Alpha-1-AT* levels among COPD and control group with different genotypes. For the rs1051052 polymorphism, *Alpha-1-AT* levels were the highest among COPD patients with AA genotype, followed by patients with AG and GG genotypes ($\chi^2 = 122.45$, $P < 0.001$). Similar trend was also observed in control group ($\chi^2 = 23.67$, <0.001). For rs1243166 polymorphism, *Alpha-1-AT* levels were

Table 1: Comparison of clinical characteristics between COPD and control groups

Variable	Control group ($n = 198$)	COPD group ($n = 225$)	χ^2 or t	P
Gender (male/female), *n*	99/99	120/105	0.469	0.338
Age (years), mean ± SD	66.8 ± 9.4	66.0 ± 8.5	0.919	0.384
Height (cm), mean ± SD	167.1 ± 6.9	165.6 ± 7.1	2.197	0.027
Weight (kg), mean ± SD	69.9 ± 13.9	70.9 ± 10.7	0.834	0.433
BMI (kg/m^2)	25.0 ± 4.5	25.7 ± 3.8	11.821	0.063
Smoker, *n*	30	37	0.132	0.680
Passive smoking, *n*	18	32	2.661	0.103
Biofuels exposure, *n*	88	102	0.034	0.776
Occupational dust exposure*, *n*	5	16	4.694	0.030
Animal dust exposure†, *n*	62	84	1.698	0.194

*Coal dust, cement dust, welding fume; †Dove, cattle, and sheep fur. COPD: Chronic obstructive pulmonary disease; SD: Standard deviation; BMI: Body mass index.

the highest among COPD patients with AG genotype, followed by AA and GG genotype (χ^2 = 11.89, P = 0.003). However, no significant difference was observed in control group (χ^2 = 3.26, P = 0.196). With regard to rs9944115 genotype, both COPD and control groups showed no significant difference in *Alpha-1-AT* levels among different genotypes [Table 4].

Discussion

The development of COPD is partially caused by genetic factors. Some analyses also identified interacting genes that might play a role in COPD pathogenesis. These genes include *SERPINE2*, *CD79A*, and *POU2AF1*.[11] In the current study, we observed that *Alpha-1-AT* is a susceptibility gene associated with COPD. Genes encoding Alpha-1-AT are located on chromosomes 14q31.0–32.3, 12.2 kb in length. Mature Alpha-1-AT is composed of a single peptide chain containing 394 amino acids, molecular weight to be approximately 52,000 Da, nine alpha helices, and three beta folds. Alpha-1-AT interacts with the protease to form a 1:1 tight structure and develop the inhibitory function of the protease.[12] The percentage of *Alpha-1-AT* genotypes in normal Saudi individuals was 17%, 2%, 0.2%, 0.8%, and 0% for MS, MZ, ZZ, SZ, and SS genotypes, respectively. The mean value of serum Alpha-1-AT levels was normal in these individuals.[13] Previous studies have shown that Alpha-1-AT expression in different geographical regions and ethnicities influences the occurrence and development of COPD. However, the polymorphism of other loci of the gene also influences the development of COPD, which needs further studies. The previous concept that genetic polymorphisms are in the exon region and can lead to variations in the amino acids in vital parts of the protein causing functional alterations and that the polymorphism in the regulation region might affect the level of gene expression, indicates the physiological significance of these two types of SNPs, and forms the core of the study of the susceptibility genes in polygenic disease. The 3' UTR, which is located in the coding region, is known as the translation section 3' end. It combines with miRNA to modulate the level of transcription after degradation of mRNA or inhibits translation to regulate the gene expression. Therefore, the number of studies on the relationship between the SNPs in the 3' UTR and the disease is increasing gradually. Since the occurrence of COPD is affected by many factors such as environment, genetic susceptibility, and racial difference, the results of a single gene locus cannot completely explain the complex pathogenesis.[14] In the case of individuals without damage, the individuals with mutant and without mutant can maintain normal *Alpha-1-AT* levels and protect the lung tissue from injury. However, under the state of stress, such as infection, inhalation of harmful components in the environment, and chronic inflammation, the level of Alpha-1-AT in the mutant individuals does not increase with the increasing of the damaging factors (such as protease), thereby it unable to protect the lung tissue effectively. Repeated stress-induced damage was accumulated gradually, leading to COPD.[15] Zhao *et al*.[16] found that *Alpha-1-AT* 3' UTR mutation

Table 2: Distributions of rs1243166, rs9944155, and rs1051052 genotypes in COPD and control groups

Genotype	Control group (n = 198)	COPD group (n = 225)	χ^2	P
rs1243166, *n* (%)				
AA	36 (18.2)	23 (10.2)	–	–
GG/GA	162 (81.8)	202 (89.8)	5.559	0.018
A	158 (39.9)	149 (33.1)	–	–
G	238 (60.1)	301 (66.9)	4.198	0.040
rs9944155, *n* (%)				
AA	36 (18.2)	113 (50.2)	–	–
GG/GA	162 (81.8)	112 (49.8)	47.386	<0.001
A	147 (37.1)	305 (67.8)	–	–
G	249 (31.9)	145 (32.2)	79.559	<0.001
rs1051052, *n* (%)				
AA	127 (64.1)	58 (25.8)	–	–
GG/GA	71 (35.9)	167 (74.2)	62.991	<0.001
A	317 (80.1)	212 (47.1)	–	–
G	79 (19.9)	238 (52.9)	97.543	<0.001

COPD: Chronic obstructive pulmonary disease; –: Not available.

Table 3: Distributions of rs1243166, rs9944155, and rs1051052 genotypes and their association with risk of COPD

Genotype	Control group (n = 198)	Case group (n = 225)	χ^2	P	*OR*	95% *CI*
rs1243166, *n* (%)						
AA	36 (18.2)	23 (10.2)	–	–	1.000	–
GG	76 (38.4)	99 (44.0)	5.470	0.019	2.039	1.116–3.725
GA	86 (43.4)	103 (45.8)	4.330	0.037	1.875	1.033–3.404
rs9944155, *n* (%)						
AA	36 (18.2)	113 (50.2)	–	–	1.000	–
GG	87 (43.9)	33 (14.7)	62.583	<0.001	0.121	0.070–0.209
GA	75 (37.9)	79 (35.1)	19.646	<0.001	0.336	0.205–0.548
rs1051052, *n* (%)						
AA	127 (64.1)	58 (25.8)	–	–	1.000	–
AG	63 (31.8)	96 (42.7)	29.136	<0.001	3.337	2.140–5.204
GG	8 (4.0)	71 (31.5)	75.878	<0.001	19.433	8.783–43.000

COPD: Chronic obstructive pulmonary disease; *CI*: Confidence interval; *OR*: Odds ratio; –: Not available.

Table 4: Associations of Alpha-1-AT levels with genotypes in case and control groups

Genotype	Alpha-1-AT levels	χ^2	*P*
Case group (*n* = 225)			
Rs1051052			
AA	2.13 (1.57–2.33)	–	–
AG	0.88 (0.79–1.36)	–	–
GG	0.64 (0.62–0.72)	122.45	<0.001
Rs1243166			
AA	0.77 (0.72–1.30)	–	–
AG	0.90 (0.72–1.37)	–	–
GG	0.73 (0.62–1.35)	11.89	0.003
Rs9944115			
AA	0.82 (0.64–1.36)	–	–
AG	0.84 (0.68–1.36)		
GG	2.48 (0.66–2.84)	3.29	0.193
Control group (*n* = 198)			
Rs1051052			
AA	1.09 (1.04–1.14)	–	–
AG	1.05 (1.03–1.12)	–	–
GG	0.96 (0.86–1.09)	23.67	<0.001
Rs1243166			
AA	1.05 (1.02–1.09)	–	–
AG	1.03 (0.92–1.10)	–	–
GG	1.06 (1.02–1.14)	3.26	0.196
Rs9944115			
AA	1.05 (0.96–1.13)	–	–
AG	1.03 (0.96–1.11)	–	–
GG	1.05 (1.02–1.08)	0.87	0.646

Alpha-1-AT: Alpha-1-antitrypsin; –: Not available.

significantly increased in patients with COPD and lung cancer which is the risk factor of COPD and lung cancer.

The present study selected rs1243166, rs9944155, and rs1051052 sites that were located in the 3' UTR of *Alpha-1-AT* as a candidate gene and explored their association with COPD in Uygur population of Kashgar region. The results showed that *Alpha-1-AT* gene rs1243166, rs9944155, and rs1051052 sites might be associated with the onset of COPD in Uygur population. The rs1243166-G allele was associated with a higher risk of COPD. The rs9944155-G allele might serve as a protective gene in Uyghur COPD. Uyghur individuals carrying rs1051052-G allele might have a higher risk of COPD. Alpha-1-AT levels in patients with COPD are lower. The levels of enzymes corresponding to different genotypes were different. The previous similar studies have not been able to determine whether the results are related to race or region. In addition, the sample size of this study is small and might not completely represent the gene mutation status of the whole population. Therefore, it is necessary to expand the sample size in the future study and to investigate other sites to assess the relationship between the gene mutation in the 3' UTR of *Alpha-1-AT* and the occurrence and development of COPD.

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Conflicts of interest

There are no conflicts of interest.

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喀什地区维吾尔族人群α1抗胰蛋白酶基因位点rs9944155、rs1051052和rs1243166基因多态性与慢性阻塞性肺疾病的关系

摘要

背景: 以往研究表明在不同种族、不同人群中，α-1-抗胰蛋白酶(Alpha-1-AT)的表达影响慢性阻塞性肺疾病(COPD)的发生和发展。我们研究的目的是探讨新疆维吾尔族人群中α-1-抗胰蛋白酶基因rs9944155AG、rs1051052AG、rs1243166AG多态性与COPD发病的关系。

方法: 选取2013年3月至2015年12月喀什地区第一人民医院（新疆维吾尔自治区，中国）住院收治的225例维吾尔族COPD患者作为病例组,根据成组匹配的原则(年龄，性别）收集198例维吾尔族健康体检人群作为对照组，用DNA试剂盒提取DNA，利用Sequenom MassARRAY SNP技术对α1-抗胰蛋白酶基因多态性分析，采用酶联免疫吸附试验(ELISA)检测血清α-1-抗胰蛋白酶水平。

结果: rs1243166-G等位基因与COPD的发病风险有关(*OR*=2.039, 95%*CI*: 1.116-3.725, *P*=0.019)。在病例组中，携带rs1243166 AG基因型的患者α-1-AT水平较高，AA和GG基因型比较低 (χ^2 = 11.89, *P* = 0.003)。同样，rs1051052-G等位基因有较高的患病风险(*OR* = 19.433, 95% *CI*: 8.783-43.00, *P* <0.001)。rs1051052 AA基因型α-1-抗胰蛋白酶水平较高， AG和GG基因型α-1-抗胰蛋白酶水平较低 (χ^2=122.45, *P* <0.001)。然而，携带rs9944155-G等位基因的个体患COPD的风险低于携带rs9944155-A等位基因(*OR* = 0.121, 95% *CI*: 0.070-0.209, *P* <0.001)。在病例组和对照组中，rs 9944115不同基因型之间α-1-抗胰蛋白酶水平差异无统计学意义。

结论:α1-抗胰蛋白酶基因rs1243166，rs9944155和rs1051052位点可能与维吾尔族COPD的发病有关，维吾尔族人群携带rs1243166-G等位基因、携带rs1051052-G等位基因可能有较高的患病风险。rs9944155-G等位基因是维吾尔族COPD的保护基因。CODP患者α-1-抗胰蛋白酶水平低于健康对照组，在病例组中rs1051052-AG基因型和rs1243166-AG 基因型对应的α-1-抗胰蛋白酶水平也不同。