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Genetic polymorphisms in *MIR1208* and *MIR5708* are associated with susceptibility to COPD in the Chinese population

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Abstract
Background: Chronic obstructive pulmonary disease (COPD) is a complex disease characterized by limited airflow and is influenced by genetic and environmental factors. The purpose of this study was to investigate the effects of gene polymorphisms in *MIR5708* and *MIR1208* on COPD risk.
Methods: Four single nucleotide polymorphisms (SNPs) in *MIR5708* (rs6473227 and rs16907751) and *MIR1208* (rs2608029 and rs13280095) were selected and genotyped among 315 COPD patients and 314 healthy controls using the Agena MassARRAY platform. SPSS 18.0 was used for statistical analysis and data processing. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the association between genetic variants of *MIR1208* and *MIR5708* and COPD risk.
Results: The results suggested that rs16907751 variants in *MIR5708* contributed to an increased susceptibility to COPD in the allelic ($P = 0.001$), co-dominant (homozygous) ($P = 0.001$), dominant

Abbreviations: COPD, chronic obstructive pulmonary disease; miRNAs, micro RNAs; SNPs, single nucleotide polymorphisms; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium; BMI, body mass index; RR, respiratory rate; PR, pulse rate.

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(P = 0.017), recessive (P = 0.002), and additive (P = 0.002) models. The effects of *MIR5708* and *MIR1208* gene polymorphisms on the risk of COPD were age-, sex-, smoking status-, and BMI-related. Furthermore, the C-A and G-A haplotypes of rs2608029 and rs13280095 in *MIR1208* were identified as risk factors for COPD in the population over 70 years (P = 0.029) and in women (P = 0.049), respectively. Finally, significant associations between rs16907751genotypes with pulse rate and forced expiratory volume in 1 s were found among COPD patients.

Conclusion: Genetic polymorphisms in *MIR5708* and *MIR1208* are associated with increased risk of COPD in China.

Introduction

Chronic obstructive pulmonary disease (COPD) is a multifactorial chronic respiratory disease characterized by irreversible pulmonary airflow obstruction.[1,2] Many studies have shown that the development of COPD is influenced by environmental factors and a complex set of genetic traits.[2—4] Recently, genome-wide association and exome sequencing studies have been used to identify the hereditary factors of COPD among different populations, but the effect of genetic variants on COPD is still unclear.[5]

Micro RNAs (miRNAs) are a class of endogenous non-coding RNAs, 22—25 nucleotides in length that can bind to the 3′-UTR region of mRNA transcripts, thereby inhibiting their translation and expression.[6,7] Variants in miRNAs are thought to be involved in post-transcriptional regulation and influence disease susceptibility.[7,8] Zhou et al and Wang et al found that the miR-146a rs2910164 single nucleotide polymorphism (SNP) is associated with improved lung function in smokers with COPD.[7,8] Related studies in the Korean population have suggested that gene polymorphisms in miR-196a2, miR-146a, and miR-499 could be associated with asthma phenotypes.[6] Fawzy et al also found a significant association between the miR-196a2 rs11614913 polymorphism and the bronchodilator response in Egyptians with COPD.[9] Therefore, it is important to explore the effect of miRNA variants on susceptibility to COPD.

MIR5708 and *MIR1208* are miRNAs located on chromosome 8. *MIR5708* has been identified as a risk locus for rheumatoid arthritis through gene-based association testing.[10] *MIR1208* is thought to be involved in the regulation of tumor-related pathways by binding to the upstream gene circMTUS1.[11] Relevant studies have also recognized *MIR1208* as a tumor suppressor gene that can increase sensitivity of renal cancer cells to cisplatin.[12] Moreover, genetic polymorphisms of *MIR1208* rs2648841 have been found to be related to chemotherapy toxicity in children with acute lymphoblastic leukemia.[13] However, to the best of our knowledge, the influence of *MIR5708* and *MIR1208* polymorphisms on the risk of COPD has not been studied.

Therefore, we performed this case-control study to investigate the relationship between *MIR5708* (rs6473227 and rs16907751) and *MIR1208* (rs2608029 and rs13280095) polymorphisms and susceptibility of Chinese to COPD, and to explain the roles of genetic factors in the pathogenesis of COPD through statistical analysis.

Methods

Study population

This study recruited 314 COPD patients (76% men) and 315 healthy controls (75% men). Patients with appropriate symptoms including dyspnea, cough, sputum production, wheezing, and chest tightness were considered as suspected cases of COPD, which were further confirmed by a post-bronchodilator fixed ratio of forced expiratory volume in 1 second/-forced vital capacity (FEV_1/FVC) < 0.70.[14] Meanwhile, patients with other respiratory diseases, autoimmune diseases, cardiovascular diseases, and others were excluded. Healthy controls were recruited from the physical examination center of Hainan General Hospital, matched by age and sex with $FEV_1/FVC > 0.70$, and no disease or family history. Demographic and clinical characteristics of all subjects were surveyed, and informed consent was obtained regarding the purpose and procedure of this study. This study was approved by the Hainan General Hospital and followed the Declaration of Helsinki guidelines.

SNP selection and genotyping

The selection of SNPs was based on haplotype or genotype data. Two SNPs in *MIR1208* (rs2608029 and rs13280095) and two in *MIR5708* (rs6473227 and rs16907751) were selected from the database of the 1000 Genomes Project (https://www.internationalgenome.org/) with the criteria of minor allele frequency (MAF) > 0.05, and $r^2 > 0.80$. The online design of the corresponding primers was performed in AgenaCx Tools (https://agenacx.com/online-tools/), and the primer sequences are listed in Supplementary Table 1. Genomic DNA of all participants was extracted and purified from cryopreserved serum using a GoldMag-Beads Kit (GoldMag, Xi'an, Shaanxi, China), and spectrophotometry (Beckman, Fullerton, CA, USA) was used to determine DNA concentration. SNP genotyping and data collection were conducted using the Agena MessARRAY platform and Agena Bioscience TYPER software (Agena Bioscience, San Diego, CA, USA), respectively.

Statistical analysis

The statistical data of this case-control study were processed using SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA), Microsoft Excel software, and PLINK software (version 1.07) (http://www.cog-genomics.org/plink2/).

Independent-sample t-test and chi-squared test were used to assess differences in clinical indexes between COPD patients and healthy controls, where appropriate. The association between each SNP and the risk of COPD was evaluated by logistic regression analysis under different genetic models, and was represented by odds ratios (ORs) and 95 % confidence intervals (CIs) after adjusting for age and sex. Hardy-Weinberg equilibrium (HWE) for each SNP in the control group was determined using Fisher's exact test. Statistical significance was set at $p < 0.05$.

Results

Clinical indexes of participants and genotypic characteristics of selected SNPs

Demographics and clinical indexes of all 629 participants comprising 315 COPD patients (mean age 71.93 ± 10.11 years) and 314 healthy controls (mean age 71.23 ± 6.83 years old) are displayed in Table 1. Statistically, cases and controls were matched by age (P = 0.306) and sex (P = 0.908).

Table 2 lists the detailed information of the four SNPs in *MIR2708* and *MIR1208*; MAFs > 0.05 and SNPs in the control group conformed to HWE ($P > 0.05$). Moreover, a significant association between the rs16907751 polymorphism and COPD risk was found in the allelic model (P = 0.001).

Association of MIR1208 and MIR5708 polymorphisms and COPD susceptibility

We carried out an association analysis on genetic variants and COPD susceptibility and the relevant data are presented in Table 3. The results suggested that the TT genotype at rs16907751 in *MIR5708* was a risk factor for COPD in the co-dominant (OR = 4.62, 95% CI = 1.84−11.62, P = 0.001), dominant (OR = 1.49, 95% CI = 1.07−2.08, P = 0.017), recessive (OR = 4.27, 95% CI = 1.71−10.66, P = 0.002), and additive (OR = 1.57, 95% CI = 1.19−2.07, P = 0.002) models.

To further explore the association between SNPs and COPD risk, we conducted a stratified analysis according to age, sex, BMI, and smoking status. According to the data listed in Table 4, rs6473227 in *MIR5708* was associated with an increased risk of COPD in the population with a body mass index (BMI, kg/m^2) less than or equal to 24 in the allelic (OR = 1.66, 95% CI = 1.13−2.44, P = 0.010), homozygous co-dominant (OR = 2.97, 95% CI = 1.34−6.62, P = 0.008), recessive (OR = 2.15, 95% CI = 1.06−4.35, P = 0.033), and additive (OR = 1.72, 95% CI = 1.16−2.55, P = 0.007) models. Moreover, rs16907751 in *MIR5708* was found to be significantly associated with an increased risk of COPD in males, non-smokers, patients older than 70 years, and individuals with a BMI ≤ 24. In addition, females heterozygous at rs2608029 (OR = 2.24, 95% CI = 1.09−4.64, P = 0.029) were more susceptible to COPD risk in both dominant (OR = 2.19, 95% CI = 1.07−4.47, P = 0.031) and additive (OR = 1.99, 95% CI = 1.02−3.91, P = 0.045) models.

We continued with a haplotype analysis and found a block (rs2608029 and rs13280095) in *MIR1208* (Table 5). The C-A haplotype of rs2608029 and rs13280095 was found to be related to an increased risk of COPD (OR = 2.59, 95% CI = 1.10−6.06, P = 0.029) in the population over 70 years, whereas $G_{rs2608029}A_{rs13280095}$ was found to be a risk factor for COPD in women.

Association analysis of clinical indexes of COPD and gene polymorphisms

Then, the effects of genetic variants in *MIR5708* and *MIR1208* on COPD were investigated in terms of clinical indices, including respiratory rate (RR), pulse rate (PR), FVC, FEV_1, and FEV_1/FVC (Table 6). The results suggested that rs16907751 in *MIR5708* was significantly associated with PR (P = 0.009) and FEV_1 (P = 0.049) in the genotypic model.

Table 1 Clinical characteristics of cases and controls.

Variables	Case (n = 315)	Control (n = 314)	P
Age (Mean ± SD)	71.93 ± 10.11	71.23 ± 6.83	0.306[a]
≤ 70	127 (40%)	137 (44%)	
> 70	188 (60%)	177 (56%)	
Gender			0.908[b]
Male	239 (76%)	237 (75%)	
Female	76 (24%)	77 (25%)	
BMI (kg/m^2)			
≤ 24	251 (80%)	67 (21%)	
> 24	29 (9%)	78 (25%)	
Tobacco smoking status			
Yes	147 (47%)	52 (17%)	
No	166 (53%)	118 (38%)	
Comorbidity			
Yes	93 (30%)		
No	174 (55%)		

SD, standard deviation; BMI, body mass index.
[a] P was calculated by t test.
[b] P was calculated by Pearson's chi-squared test.

Table 2 Information regarding SNPs in *MIR5708* and *MIR1208*.

Gene	SNP	Chromosome	Position	Allele A/B	MAF		HWE-*P*	OR(95% CI)	*P*
					Case	Control			
MIR5708	rs6473227	8	81285892	A/C	0.448	0.462	0.651	0.94(0.76−1.18)	0.614
MIR5708	rs16907751	8	81375457	T/C	0.238	0.164	0.411	1.59(1.20−2.11)	0.001
MIR1208	rs2608029	8	129170126	C/G	0.167	0.145	0.648	1.18(0.87−1.60)	0.298
MIR1208	rs13280095	8	129179090	C/A	0.116	0.112	1	1.04(0.73−1.48)	0.821

SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; 95% CI, 95% confidence interval.
Bold $P < 0.05$ indicates statistical significance.

Table 3 Association of *MIR5708* and *MIR1208* polymorphisms with COPD risk.

SNP	Model	Allele/Genotype	Case	Control	OR(95% CI)	*P*
rs6473227	Co-dominant (HOM)	AA vs CC	65(20.6%)	69(22.0%)	0.88(0.57−1.38)	0.584
	Co-dominant (HET)	AC vs CC	152(48.3%)	152(48.4%)	0.94(0.65−1.35)	0.724
	Dominant	AA-AC vs CC	217(68.9%)	221(70.4%)	0.92(0.65−1.29)	0.632
	Recessive	AA vs AC-CC	65(20.6%)	69(22.0%)	0.92(0.63−1.35)	0.669
	Additive				0.94(0.75−1.17)	0.579
rs16907751	Co-dominant (HOM)	TT vs CC	23(7.3%)	6(1.9%)	4.62(1.84−11.62)	0.001
	Co-dominant (HET)	TC vs CC	101(32.1%)	91(29.0%)	1.29(0.91−1.82)	0.149
	Dominant	TT-TC vs CC	124(39.4%)	97(30.9%)	1.49(1.07−2.08)	0.017
	Recessive	TT vs TC-CC	23(7.3%)	6(1.9%)	4.27(1.71−10.66)	0.002
	Additive				1.57(1.19−2.07)	0.002
rs2608029	Co-dominant (HOM)	CC vs GG	5(1.6%)	5(1.6%)	1.13(0.32−3.97)	0.852
	Co-dominant (HET)	CG vs GG	95(30.1%)	81(25.8%)	1.26(0.89−1.79)	0.199
	Dominant	CC-CG vs GG	100(31.7%)	86(27.4%)	1.25(0.89−1.77)	0.202
	Recessive	CC vs CG-GG	5(1.6%)	5(1.6%)	1.05(0.30−3.68)	0.940
	Additive				1.21(0.88−1.67)	0.233
rs13280095	Co-dominant (HOM)	CC vs AA	3(1.0%)	4(1.3%)	0.82(0.18−3.71)	0.792
	Co-dominant (HET)	CA vs AA	67(21.3%)	62(19.7%)	1.11(0.75−1.64)	0.608
	Dominant	CC-CA vs AA	70(22.2%)	66(21.0%)	1.09(0.74−1.60)	0.656
	Recessive	CC vs CA-AA	3(1.0%)	4(1.3%)	0.80(0.18−3.61)	0.768
	Additive				1.06(0.75−1.52)	0.731

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; HOM, homozygous; HET, heterozygous
P value was calculated by logistic regression analysis with adjustment for age and sex.
Bold $P < 0.05$ indicates statistical significance.

Furthermore, no association was found between rs6473227, rs2608029, and rs13280095 and the clinical indices of COPD.

Discussion

According to the latest Global Health Observatory data, COPD was ranked as the third leading cause of death worldwide, accounting for approximately 5% of all deaths globally in 2015 (3.17 million deaths). The prevalence and burden of COPD are projected to increase over the coming decades.[15] It has been clearly demonstrated that the interaction between genotype and environment plays an important role in COPD phenotypes.[16,17] Genetic background plays a critical role in the development of COPD, and related studies have proposed significant differences in genetic susceptibility to COPD among different races and ethnicities.[18] Therefore, the effect of genetic polymorphisms of candidate genes on the risk of COPD among Chinese was examined.

As a result, statistical analysis of the genotyping results of 315 COPD patients and 314 healthy controls among Chinese patients identified *MIR5708* rs16907751 as a risk factor of COPD, and significant associations between rs16907751 and clinical indexes including PR and FEV_1 in COPD patients were found. The examined mutation loci have been rarely reported; only rs6473227 showed a close relationship with atopic dermatitis in a related case-control analysis.[19] Our results suggest that rs6473227 may contribute to an increased risk of COPD in individuals with a BMI less than 24. A related study pointed out that neuroimmune interactions are implicated in chronic inflammations such as atopic dermatitis, COPD, and asthma[20]; therefore, we hypothesized that *MIR5708* rs6473227 may increase susceptibility to inflammation-related disorders. In addition, we found that *MIR5708* rs16907751 may increase the risk of COPD in patients with normal BMI. There have been studies supporting our findings and reported that low BMI is a risk factor for accelerated decline in lung function compared to normal

Table 4 Stratification analysis of the associations between *MIR1208* and *MIR5708* polymorphisms and COPD risk.

SNP	Model	Age >70		Male		Female		Non-Smoking		BMI ≤24	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
rs6473227	Allele	0.91(0.68−1.22)	0.546	0.96(0.74−1.24)	0.753	0.90(0.57−1.41)	0.637	0.84(0.60−1.17)	0.300	1.66(1.13−2.44)	0.010
	Co-dominant (HOM)	0.75(0.40−1.39)	0.353	0.93(0.55−1.55)	0.771	0.79(0.33−1.91)	0.596	0.71(0.36−1.37)	0.306	2.97(1.34−6.62)	0.008
	Co-dominant (HET)	1.08(0.66−1.79)	0.756	0.89(0.59−1.36)	0.604	1.09(0.52−2.26)	0.818	0.84(0.48−1.45)	0.527	1.68(0.89−3.18)	0.107
	Dominant	0.97(0.61−1.56)	0.905	0.90(0.61−1.34)	0.618	0.98(0.50−1.94)	0.958	0.79(0.47−1.33)	0.378	1.16(0.66−2.07)	0.603
	Recessive	0.71(0.42−1.20)	0.203	0.99(0.64−1.55)	0.976	0.75(0.35−1.62)	0.462	0.79(0.44−1.40)	0.413	2.15(1.06−4.35)	0.033
	Additive	0.88(0.65−1.20)	0.413	0.96(0.74−1.24)	0.734	0.90(0.58−1.40)	0.651	0.84(0.60−1.17)	0.302	1.72(1.16−2.55)	0.007
rs16907751	Allele	2.00(1.36−2.95)	<0.001	1.63(1.18−2.26)	0.003	1.47(0.84−2.59)	0.179	1.62(1.03−2.56)	0.036	1.67(1.00−2.78)	0.047
	Co-dominant (HOM)	16.14(2.03−128.4)	0.009	4.64(1.68−12.78)	0.003	4.63(0.50−42.97)	0.178	−	−	2.90(0.64−13.16)	0.168
	Co-dominant (HET)	1.45(0.90−2.34)	0.127	1.27(0.85−1.90)	0.238	1.30(0.66−2.57)	0.448	1.10(0.64−1.88)	0.723	1.48(0.79−2.78)	0.225
	Dominant	1.75(1.10−2.77)	0.018	1.51(1.03−2.21)	0.036	1.43(0.74−2.78)	0.286	1.36(0.81−2.29)	0.249	2.03(1.12−3.67)	0.020
	Recessive	14.47(1.83−114.70)	0.011	4.31(1.58−11.79)	0.004	4.22(0.46−38.70)	0.203	−	−	2.59(0.57−11.64)	0.216
	Additive	1.89(0.65−1.20)	0.002	1.58(1.15−2.18)	0.005	1.51(0.84−2.70)	0.171	1.57(0.99−2.47)	0.054	1.57(0.95−2.59)	0.079
rs2608029	Allele	1.05(0.68−1.61)	0.837	1.02(0.72−1.45)	0.924	1.86(0.99−3.50)	0.053	0.94(0.61−1.47)	0.800	1.11(0.66−1.87)	0.688
	Co-dominant (HOM)	1.42(0.08−23.83)	0.810	1.08(0.26−4.42)	0.916	1.30(0.08−21.55)	0.855	0.32(0.06−1.70)	0.180	0.44(0.09−2.11)	0.304
	Co-dominant (HET)	1.03(0.63−1.68)	0.918	1.05(0.70−1.57)	0.827	2.24(1.09−4.64)	0.029	1.22(0.71−2.09)	0.467	1.79(0.92−3.46)	0.085
	Dominant	1.03(0.63−1.69)	0.894	1.05(0.70−1.56)	0.817	2.19(1.07−4.47)	0.031	1.10(0.66−1.85)	0.717	1.27(0.72−2.24)	0.402
	Recessive	1.41(0.08−23.61)	0.813	1.06(0.26−4.34)	0.931	1.01(0.06−16.59)	0.994	0.30(0.06−1.58)	0.155	0.37(0.08−1.75)	0.209
	Additive	1.04(0.65−1.67)	0.867	1.04(0.73−1.50)	0.815	1.99(1.02−3.91)	0.045	0.97(0.61−1.53)	0.896	1.28(0.74−2.22)	0.384
rs13280095	Allele	0.74(0.45−1.23)	0.247	0.89(0.60−1.33)	0.576	1.67(0.82−3.40)	0.156	0.77(0.46−1.28)	0.308	1.08(0.58−2.00)	0.816
	Co-dominant (HOM)	−	−	0.72(0.12−4.39)	0.718	1.15(0.07−18.97)	0.923	0.32(0.06−2.03)	0.247	0.38(0.05−2.85)	0.343
	Co-dominant (HET)	0.69(0.39−1.22)	0.203	0.93(0.59−1.46)	0.760	1.91(0.86−4.26)	0.114	0.91(0.50−1.67)	0.769	1.68(0.78−3.61)	0.182
	Dominant	0.68(0.39−1.19)	0.178	0.92(0.59−1.43)	0.715	1.85(0.85−4.05)	0.122	0.84(0.47−1.49)	0.546	1.56(0.83−2.91)	0.164
	Recessive	−	−	0.73(0.12−4.45)	0.732	1.00(0.06−16.36)	0.998	0.37(0.07−2.06)	0.255	0.33(0.04−2.51)	0.287
	Additive	0.67(0.39−1.17)	0.159	0.92(0.61−1.38)	0.675	1.68(0.82−3.47)	0.158	0.80(0.48−1.32)	0.375	1.24(0.66−2.35)	0.508

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; HOM, homozygous; HET, heterozygous
"-" indicates no results.
P value was calculated by logistic regression analysis with adjustment for age and sex.
Bold $P < 0.05$ indicates statistical significance.

Table 5 Haplotype analysis of the association between *MIR5708* and *MIR1208* polymorphisms and COPD risk.

Gene	SNP	Subgroup	Haplotype	Fre-case	Fre-control	OR(95% CI)	*P*
MIR1208	rs2608029|rs13280095	Overall	CC	0.116	0.111	1.08(0.76−1.54)	0.681
			CA	0.051	0.034	1.55(0.88−2.73)	0.128
			GA	0.167	0.146	1.21(0.88−1.66)	0.242
MIR1208	rs2608029|rs13280095	Age (>70)	CC	0.080	0.105	0.67(0.38−1.16)	0.155
			CA	0.053	0.023	2.59(1.10−6.06)	0.029
			GA	0.133	0.128	1.04(0.65−1.67)	0.867
MIR1208	rs2608029|rs13280095	Female	CC	0.145	0.086	1.82(0.87−3.80)	0.110
			CA	0.053	0.026	2.13(0.61−7.41)	0.237
			GA	0.197	0.118	1.96(1.00−3.86)	0.049

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index
P value was calculated by logistic regression analysis with adjustment for age and sex.
Bold $P < 0.05$ indicates statistical significance

Table 6 Association analysis on the clinical indexes of COPD and gene polymorphisms.

SNP		RR (breaths/min)	PR (beats/min)	FVC (L)	FEV_1 (L)	FEV_1/FVC (%)
rs6473227	AA	22.00 ± 2.44	84.44 ± 9.36	3.30 ± 1.78	1.21 ± 0.55	31.65 ± 30.57
	CA	22.42 ± 2.43	87.28 ± 12.34	1.95 ± 0.74	1.24 ± 0.55	40.08 ± 29.36
	CC	22.33 ± 2.55	86.06 ± 11.96	1.99 ± 0.60	1.19 ± 0.49	46.26 ± 27.17
	P	0.543	0.286	0.164	0.907	0.078
rs16907751	TT	23.35 ± 3.05	93.90 ± 12.96	1.95 ± 0.80	0.99 ± 0.35	36.96 ± 27.96
	TC	22.10 ± 2.42	85.93 ± 13.06	1.90 ± 0.50	1.11 ± 0.40	41.70 ± 27.62
	CC	22.28 ± 2.41	85.54 ± 10.44	2.49 ± 4.70	1.31 ± 0.68	39.79 ± 30.68
	P	0.123	0.009	0.639	0.049	0.866
rs2608029	CC	22.60 ± 3.05	83.60 ± 5.18	2.35 ± 0.78	1.53 ± 0.83	49.21 ± 33.36
	GC	22.43 ± 2.45	88.06 ± 10.13	1.86 ± 0.71	1.19 ± 0.58	44.47 ± 30.47
	GG	22.24 ± 2.47	85.62 ± 12.38	2.45 ± 4.54	1.22 ± 0.60	37.24 ± 28.53
	P	0.812	0.239	0.640	0.558	0.276
rs13280095	AA	22.26 ± 2.53	85.98 ± 12.18	2.39 ± 4.28	1.22 ± 0.60	38.27 ± 28.97
	CA	22.36 ± 2.18	87.64 ± 9.82	1.85 ± 0.69	1.19 ± 0.58	42.96 ± 30.68
	CC	24.67 ± 1.53	86.67 ± 4.16	2.45 ± 0.92	1.70 ± 0.92	65.46 ± 9.31
	P	0.239	0.629	0.740	0.367	0.215

RR, respiratory rate; PR, pulse rate; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s.
Bold $P < 0.05$ indicates statistical significance.

BMI,[21] thereby suggesting a protective role of high BMI in COPD patients.

Tobacco smoking is widely recognized as the most important risk factor for COPD,[22] but it is not the only risk factor for COPD. Qian et al. concluded that both non-smokers and smokers are likely to suffer from COPD, which may be the result of differential miRNA expression between.[23] At present, there has been no report on the association between miR5708 and miR1208 and the risk of disease COPD. However, our study further provided evidence that allele T of *MIR5708* rs16907751 may increase susceptibility of non-smokers to COPD. There have been reports confirming that up to 30% of patients with COPD do not have a smoking history.[18] Therefore, multiple genes and exposure to environmental and occupational factors are thought to jointly affect COPD development.

Furthermore, we also found that the effects of *MIR5708* and *MIR1208* on the risk of COPD were age- and sex-dependent. Related epidemiological studies have shown that the prevalence of COPD increases with age,[24] and Mercado et al. also showed that aging of the lung resulted in loss of lung elasticity and reduced ability to respond to environmental stress and damage.[25] Our findings also indicated *MIR5708* rs16907751 as a risk factor for COPD in patients over 70 years of age. Based on the stratified analysis, our results suggested that *MIR5708* rs16907751 and *MIR1208* rs2608029 are associated with increased COPD risk in men and women, respectively, and further confirmed gender differences in COPD susceptibility conferred by these two SNPs. Aryal et al. stated that the differences in sex were derived mainly by smoking status, hormone levels, and behavioral differences.[26] Current data indicate that in China, the prevalence of COPD in men is higher than that in women, but the difference varies with exposure to risk factors and socioeconomic development in different geographic regions.[27,28] However, in our current study, we did not focus on the effect of environment, occupational differences, and regional constraints. Moreover, the small sample size and incomplete sample information in some cases are also limitations of our study. Subsequent functional experiments are needed to verify the effects of these SNPs on COPD.

Conclusion

In summary, this study is the first to indicate that genetic variants in *MIR5708* and *MIR1208* are associated with an increased risk of COPD in the Chinese population, and the effects of these SNPs are related to age, sex, smoking status, and BMI.

Conflicts of interest

All authors declared no conflict of interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pulmoe.2021.07.004.

References

1. Reséndiz-Hernández JM, Falfán-Valencia R. Genetic polymorphisms and their involvement in the regulation of the inflammatory response in asthma and COPD. Adv Clin Exp Med. 2018;27(1):125–33.
2. Li Y, Cho MH, Zhou X. What do polymorphisms tell us about the mechanisms of COPD? Clin Sci. 2017;131(24):2847–63.
3. Ding Y, Xu H, Yao J, et al. Association between RTEL1 gene polymorphisms and COPD susceptibility in a Chinese Han population. Int J Chron Obstruct Pulmon Dis. 2017;12:931–6.
4. Yuan C, Chang D, Lu G, Deng X. Genetic polymorphism and chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2017;12:1385–93.
5. Ding Y, Li Q, Wu C, et al. TERT gene polymorphisms are associated with chronic obstructive pulmonary disease risk in the Chinese Li population. Mol Genet Genomic Med. 2019;7(8):e773.
6. Trinh HKT, Pham DL, Kim SC, Kim RY, Park HS, Kim SH. Association of the miR-196a2, miR-146a, and miR-499 Polymorphisms with asthma phenotypes in a Korean population. Mol Diagn Ther. 2017;21(5):547–54.
7. Zhou S, Liu Y, Li M, et al. Combined effects of PVT1 and MiR-146a single nucleotide polymorphism on the lung function of smokers with chronic obstructive pulmonary disease. Int J Biol Sci. 2018;14(10):1153–62.
8. Wang R, Li M, Zhou S, et al. Effect of a single nucleotide polymorphism in miR-146a on COX-2 protein expression and lung function in smokers with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2015;10:463–73.
9. Fawzy MS, Hussein MH, Abdelaziz EZ, Yamany HA, Ismail HM, Toraih EA. Association of MicroRNA-196a2 variant with response to short-acting β2-agonist in COPD: an egyptian pilot study. PLoS One. 2016;11(4):e0152834.
10. Lenert A, Fardo DW. Detecting novel micro RNAs in rheumatoid arthritis with gene-based association testing. Clin Exp Rheumatol. 2017;35(4):586–92.
11. Shang Q, Li Y, Wang H, Ge S, Jia R. Altered expression profile of circular RNAs in conjunctival melanoma. Epigenomics. 2019;11(7):787–804.
12. Kim EA, Jang JH, Sung EG, Song IH, Kim JY, Lee TJ. MiR-1208 increases the sensitivity to cisplatin by targeting TBCK in renal cancer cells. Int J Mol Sci. 2019;20(14).
13. Gutierrez-Camino A, Umerez M, Santos B, et al. Pharmacoepigenetics in childhood acute lymphoblastic leukemia: involvement of miRNA polymorphisms in hepatotoxicity. Epigenomics. 2018;10(4):409–17.
14. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195(5):557–82.
15. Labaki WW, Rosenberg SR. Chronic obstructive pulmonary disease. Ann Int Med. 2020;173(3):Itc17–32.
16. Agustí A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. N Eng J Med. 2019;381(13):1248–56.
17. Corlateanu A, Mendez Y, Wang Y, Garnica RJA, Botnaru V, Siafakas N. Chronic obstructive pulmonary disease and phenotypes: a state-of-the-art. Pulmonology. 2020;26(2):95–100.
18. Ma Y, Tong X, Liu Y, Liu S, Xiong H, Fan H. ACE gene polymorphism is associated with COPD and COPD with pulmonary hypertension: a meta-analysis. Int J Chron Obstruct Pulmon Dis. 2018;13:2435–46.
19. Kim JH, Lee SY, Kang MJ, et al. Association of genetic polymorphisms with atopic dermatitis, clinical severity and total IgE: a replication and extended study. Allergy Asthma Immunol Res. 2018;10(4):397–405.
20. Blake KJ, Jiang XR, Chiu IM. Neuronal regulation of immunity in the skin and lungs. Trends Neurosci. 2019;42(8):537–51.
21. Sun Y, Milne S, Jaw JE, et al. BMI is associated with FEV(1) decline in chronic obstructive pulmonary disease: a meta-analysis of clinical trials. Respir Res. 2019;20(1):236.
22. Wang L, Tang Y, Chen Y. HIF1A gene rs10873142 polymorphism is associated with risk of chronic obstructive pulmonary disease in a Chinese Han population: a case-control study. Biosci Rep. 2018;38(2):BSR20171309.
23. Qian Y, Mao ZD, Shi YJ, Liu ZG, Cao Q, Zhang Q. Comprehensive analysis of miRNA-mRNA-lncRNA networks in non-smoking and smoking patients with chronic obstructive pulmonary disease. Cell Physiol Biochem. 2018;50(3):1140–53.
24. Raherison C, Girodet PO. Epidemiology of COPD. Eur Respir Rev. 2009;18(114):213–21.
25. Mercado N, Ito K, Barnes PJ. Accelerated ageing of the lung in COPD: new concepts. Thorax. 2015;70(5):482–9.
26. Aryal S, Diaz-Guzman E, Mannino DM. COPD and gender differences: an update. Transl Res. 2013;162(4):208–18.
27. Zhu B, Wang Y, Ming J, Chen W, Zhang L. Disease burden of COPD in China: a systematic review. Int J Chron Obstruct Pulmon Dis. 2018;13:1353–64.
28. Ntritsos G, Franek J, Belbasis L, et al. Gender-specific estimates of COPD prevalence: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2018;13:1507–14.