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LINC01414/LINC00824 genetic polymorphisms in association with the susceptibility of chronic obstructive pulmonary disease

Xiaoman Zhou[†], Yunjun Zhang[†], Yutian Zhang, Quanni Li, Mei Lin, Yixiu Yang, Yufei Xie and Yipeng Ding^{*}

Abstract

Objective: Chronic obstructive pulmonary disease (COPD) is a complicated multi-factor, multi-gene disease. Here, we aimed to assess the association of genetic polymorphisms in *LINC01414/LINC00824* and interactions with COPD susceptibility.

Methods: Three single nucleotide polymorphisms (SNPs) in *LINC01414/LINC00824* was genotyped by Agena MassAR-RAY platform among 315 COPD patients and 314 controls. Logistic analysis adjusted by age and gender were applied to estimate the genetic contribution of selected SNPs to COPD susceptibility.

Results: *LINC01414* rs699467 (OR = 0.73, 95% CI 0.56–0.94, p = 0.015) and *LINC00824* rs7815944 (OR = 0.56, 95% CI 0.31–0.99, p = 0.046) might be protective factors for COPD occurrence, while *LINC01414* rs298207 (OR = 2.88, 95% CI 1.31–6.31, p = 0.008) risk-allele was related to the increased risk of COPD in the whole population. Rs7815944 was associated with the reduced risk of COPD in the subjects aged > 70 years (OR = 0.29, p = 0.005). Rs6994670 (OR = 0.57, p = 0.007) contribute to a reduced COPD risk, while rs298207 (OR = 7.94, p = 0.009) was related to a higher susceptibility to COPD at age \leq 70 years. Rs298207 (OR = 2.54, p = 0.043) and rs7815944 (OR = 0.43, p = 0.028) variants was associated COPD risk among males. Rs7815944 (OR = 0.16, p = 0.031) was related to the reduced susceptibility of COPD in former smokers. Moreover, the association between rs298207 genotype and COPD patients with dyspnea was found (OR = 0.50, p = 0.016), and rs7815944 was related to COPD patients with wheezing (OR = 0.22, p = 0.008).

Conclusion: Our finding provided further insights into *LINC01414/LINC00824* polymorphisms at risk of COPD occurrence and accumulated evidence for the genetic susceptibility of COPD.

Keywords: Chronic obstructive pulmonary disease, *LINC01414/LINC00824*, Polymorphism, Smoking status, Clinical symptom

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Introduction

Chronic obstructive pulmonary disease (COPD) is a severely disabling chronic lung disease. COPD is characterized by persistent airflow limitation of respiratory systems due to emphysema and obstructive bronchiolitis [1]. The airflow limitation is caused by the large exposure of lung to harmful particles or gases. At present, the high incidence of COPD exceeds 250 million, which

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Variable	Cases	Controls	p
n	315	314	
Age, (mean \pm SD) year	71.9 ± 10.1	71.2±6.8	0.307
Gender (male/female), n	239/76	237/77	0.926
Smoking (current/former/never/unavailable), n	83/64/166/2	34/18/118/114	
BMI, (\leq 24 kg/m ² />24 kg/m ² /unavailable), n	251/29/35	67/78/169	
COPD with complication (yes/no/unavailable), n	93/174/48		
COPD with wheezing	153/123/39		
COPD with dyspnea	115/166/34		
COPD with chest distress	102/179/34		
respiratory rate, times/min	22.3 ± 2.5		
pulse rate, times/min	86.3 ± 11.7		
FVC, L	2.0 ± 0.7		
FEV1, L	1.1 ± 0.6		
FEV1/FVC, %	51.4 ± 11.8		
GOLD spirometric grade, n (%)			
1	34 (10.8%)		
2	107 (46.7%)		
3	102 (32.4%)		
4	32 (10.2%)		

Table 1 Characteristics of patients with COPD patients and controls

COPD chronic obstructive pulmonary disease, BMI body mass index, FVC including forced vital capacity, FEV1 forced the first second of expiratory volume, GOLD Global Initiative for Chronic Obstructive Lung Disease

p values were calculated by χ^2 test or the Student's t test

Gene	SNP ID	Chr: position	Alleles	MAF		Call rate (%)	HWE			OR (95% CI)	р
			(Alt/Ref)	Cases	Controls		O(HET)	E(HET)	p		
LINC01414	rs6994670	8:65,191,812	G/A	0.214	0.273	99.8	0.393	0.397	0.887	0.73 (0.56–0.94)	0.015*
LINC01414	rs298207	8:65,282,597	A/G	0.229	0.189	98.4	0.320	0.307	0.578	1.27 (0.97–1.68)	0.086
LINC00824	rs7815944	8:129,427,518	G/A	0.265	0.304	99.8	0.390	0.423	0.181	0.83 (0.65–1.06)	0.131

Table 2 The information about the candidate SNPs and the association with COPD in the allele model

Bold indicate that p < 0.05 means the data is statistically significant

COPD chronic obstructive pulmonary disease, SNP single nucleotide polymorphism, MAF minor allele frequency, HWE Hardy–Weinberg equilibrium, O(HET) observed heterozygotes, E(HET) expected heterozygotes

is the third leading cause of death in the world, and it is estimated to cause 4 million deaths every year [2, 3]. In China, COPD caused over 0.9 million deaths is related to several public health problems including pollution, an aging population, and smoking [4, 5]. COPD is a complicated multi-factor, multi-gene disease. Several studies displayed that the occurrence of COPD is associated with various factors such as tobacco smoking, air pollution, pulmonary tuberculosis, occupational exposure and genetic factors [6]. Increasing evidence suggested that genetic polymorphisms exert an important role in COPD occurrence and development [7–9].

Long non-coding RNAs (lncRNAs) is one of the key members of ncRNA family, with greater than 200

nucleotides, participating in the regulators of genetic expression and regulation [10]. Recent study has demonstrated that lncRNAs could contribute to the pathogenesis of respiratory diseases, including COPD [11]. Abnormal expression or function of lncRNAs has been considered to be involved in the development and progression of COPD [12, 13]. Recently, several studies reported some lncRNA gene polymorphisms to the susceptibility of COPD such as *PVT1*, *MiR-146a*, and *nsv823469* [14, 15]. Previously, abnormal expression of *LINC00824* was associated with smoking [16]. However, the contribution of *LINC01414/LINC00824* genetic polymorphisms to COPD predisposition remains unclear.

SNP ID	Model	Genotype	Case	Control	Adjusted by age and	l gender
					OR (95%CI)	p
LINC01414	Genotype	AA	194	166	1	
rs6994670		AG	107	123	0.75 (0.53-1.04)	0.085
		GG	14	24	0.51 (0.25-1.02)	0.056
	Dominant	AA	194	166	1	
		AG-GG	121	147	0.71 (0.51-0.97)	0.034*
	Recessive	AA-AG	301	289	1	
		GG	14	24	0.57 (0.29-1.13)	0.107
	Log-additive	-	_	-	0.73 (0.56–0.95)	0.018*
LINC01414	Genotype	GG	192	201	1	
rs298207		GA	94	99	1.00 (0.71-1.41)	0.990
		AA	24	9	2.87 (1.30-6.36)	0.009*
	Dominant	GG	192	201	1	
		GA-AA	118	108	1.15 (0.83-1.60)	0.400
	Recessive	GG-GA	286	300	1	
		AA	24	9	2.88 (1.31-6.31)	0.008*
	Log-additive	_	_	_	1.27 (0.97-1.66)	0.085
LINC00824	Genotype	AA	168	157	1	
rs7815944		AG	127	122	0.96 (0.69-1.34)	0.828
		GG	20	34	0.55 (0.30-0.99)	0.047*
	Dominant	AA	168	157	1	
		AG-GG	147	156	0.87 (0.64-1.20)	0.401
	Recessive	AA-AG	295	279	1	
		GG	20	34	0.56 (0.31–0.99)	0.046*
	Log-additive				0.83 (0.65–1.06)	0.128

Table 3 Association between candidate SNPs and COPD susceptibility

p values were calculated by logistic regression analysis adjusted by age and gender

Bold indicate that p < 0.05 means the data is statistically significant

COPD chronic obstructive pulmonary disease, SNP single nucleotide polymorphism, OR odds ratio, 95% CI 95% confidence interval

Here, we genotyped three polymorphisms in *LINC01414/ LINC00824* to assess the genetic association of variants and interactions with COPD susceptibility among the Chinese Han population. Furthermore, the heterogeneity of relationship among subgroups (defined by age, gender and smoking status) and the correlation of selected polymorphisms with clinical symptoms of COPD patients were explored.

Materials and methods

Study subjects

A total of 315 COPD patients and 314 healthy controls were enrolled in the present study from Hainan General Hospital. All subjects were ethnic Han Chinese population. COPD patients were diagnosed based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [17]. Patients with lung cancer, asthma, tuberculosis, interstitial fibrosis, bronchiectasis, and other respiratory diseases were excluded. Healthy controls who had no cancer history, respiratory diseases, inflammatory or immune diseases were recruited. We collected the demographic and clinical data of all subjects from the questionnaires and medical records. The study was approved by the medical ethics committee of Hainan General Hospital and was in the Declaration of Helsinki. All the subjects signed a written informed consent.

SNPs genotyping

Peripheral blood samples (5 mL) were collected from each subject into EDTA tubes. A commercially available DNA extraction Kits (GoldMag Co. Ltd, Xi'an, China) was used for the extraction of genomic DNA. Three single nucleotide polymorphisms (SNPs) including rs6994670 and rs298207 in *LINC01414*, rs7815944 in *LINC00824* were selected based on the minor allele frequency (MAF)>0.05 from 1000 Genomes Project database, Hardy–Weinberg equilibrium (HWE)>0.05, and the calling rate>98%. Agena MassARRAY platform (Agena, San Diego, CA, USA) performed the process of

Table 4 Association between polymorphisms and COPD risk stratified by age and gender

Age > 70 years ≤ 70 years ≤ 70 years LNC201414 Allele A 207 263 1 108 187 1 Gerotype AA 116 107 1 78 64 1 AG 65 64 0.94 (0.55-1.47) 0.76 44 1 0.31 (0.11-0.90) 0.031* CG 7 10 0.96 (0.05-1.57) 0.257 14 0.33 (0.11-0.90) 0.031* Dominant AA 16 107 0 57 (0.12-0.90) 0.052 14 0.42 (0.16-1.12) 0.063 Log-additive - 0.83 (0.57-1.36) 0.557 7 14 14 1 1 Log-additive - 0.83 (0.57-1.36) 0.557 7 14 10 1	SNP ID	Model	Genotype	Case	Control	OR (95%CI)	p	Case	Control	OR (95%CI)	р
NUMBE No. No. Signed	Age			> 70 ye	ars			≤ 70 y€	ears		
biblicity G PA PA PA PA	LINC01414	Allele	А	297	268	1		198	187	1	
Renorps AA 116 102 1 7 8 61 1 1 AG 63 64 036 (8)0A-13 0.76 42 59 05 (3) (0.72) 0.33 Deminant AA 10 102 1 7 14 0.33 (0.72) 0.33 0.33 (0.72) 0.33 0.33 (0.72) 0.33 0.33 (0.72) 0.33 0.33 (0.72) 0.33 0.33 (0.72) 0.33 0.33 (0.72) 0.33 (0.72) 0.33 0.33 (0.72) 0.33 0.33 (0.72) 0.33 0.33 (0.72) 0.33 0.33 (0.72) 0.33 0.33 (0.72) 0.33 0.33 (0.72) 0.33 (0.72) 0.33 0.33 (0.72) 0.33 <th0< td=""><td>rs6994670</td><td></td><td>G</td><td>79</td><td>84</td><td>0.85 (0.60-1.20)</td><td>0.356</td><td>56</td><td>87</td><td>0.61 (0.41-0.90)</td><td>0.012*</td></th0<>	rs6994670		G	79	84	0.85 (0.60-1.20)	0.356	56	87	0.61 (0.41-0.90)	0.012*
AG AG F AG S<		Genotype	AA	116	102	1		78	64	1	
Nome Nome <t< td=""><td></td><td></td><td>AG</td><td>65</td><td>64</td><td>0.94 (0.59–1.47)</td><td>0.776</td><td>42</td><td>59</td><td>0.57 (0.33–0.97)</td><td>0.037*</td></t<>			AG	65	64	0.94 (0.59–1.47)	0.776	42	59	0.57 (0.33–0.97)	0.037*
Nomman AAAC 16 1 - 7 6 6 1 - Recessive AAAC 3 7 1 0 0350 3 1 <td></td> <td></td> <td>GG</td> <td>7</td> <td>10</td> <td>0.56 (0.20–1.57)</td> <td>0.271</td> <td>7</td> <td>14</td> <td>0.33 (0.12–0.90)</td> <td>0.031*</td>			GG	7	10	0.56 (0.20–1.57)	0.271	7	14	0.33 (0.12–0.90)	0.031*
Receive AC-GG 7 C 7 C <thc< th=""> C <thc< th=""> C C C <thc<< td=""><td></td><td>Dominant</td><td>AA</td><td>116</td><td>102</td><td>1</td><td></td><td>78</td><td>64</td><td>1</td><td></td></thc<<></thc<></thc<>		Dominant	AA	116	102	1		78	64	1	
Recessive AAG 181 66 1 120 120 121 121 121 Log adinv GG 7 10 057021-150 0258 7 160 0007 LMC01114 GG 24 287 121034-123 0315 64 214 17 1200841 GG 180 1210 121040-125 64 20 120040-125			AG-GG	72	74	0.88 (0.57–1.36)	0.569	49	73	0.52 (0.31–0.86)	0.012*
IMC0147 INTERPORTGGG7100757 0.21-0590.2857140.42 (0.16-1.12)0.0700.070IMC0147 INTERPORTAlleleGG2424711 <td< td=""><td></td><td>Recessive</td><td>AA-AG</td><td>181</td><td>166</td><td>1</td><td></td><td>120</td><td>123</td><td>1</td><td></td></td<>		Recessive	AA-AG	181	166	1		120	123	1	
INCO1414 N2N92000 IC			GG	7	10	0.57 (0.21–1.59)	0.285	7	14	0.42 (0.16-1.12)	0.083
LINCODING Number of the sector o		Log-additive	_			0.85 (0.59–1.23)	0.385			0.57 (0.38–0.86)	0.007*
H29807AABGGG <td>LINC01414</td> <td>Allele</td> <td>G</td> <td>294</td> <td>287</td> <td>1</td> <td></td> <td>184</td> <td>214</td> <td>1</td> <td></td>	LINC01414	Allele	G	294	287	1		184	214	1	
Renergy GG IB IP I PA F2 IP PA PA PA PA PA<	rs298207		А	78	63	1.21 (0.84–1.75)	0.315	64	54	1.38 (0.91–2.08)	0.126
Res GA SA 9 124077-200 0.379 8 9 04(06.4.14) 0.20 Dominant GA 10 7 140(070-300 0.372 14 2 74(169-12) 0 Dominant GA 16 19 1 10 3 2 10(66-183) 0.20 Recssive GA 16 13 13(047-320) 0.602 13 8 10 1 10		Genotype	GG	118	119	1		74	82	1	
NA Io 7 Id0050-300 0522 Id 2 74(169-372) 0.009* Domian GGA 18 10 1 7 3 3 1			GA	58	49	1.24 (0.77–2.00)	0.379	36	50	0.84 (0.48-1.44)	0.521
Dominant GG 18 19 1 74 82 1 1 Recessive GA-M 68 56 120803-120 50 1206-133 7 Recessive GA-M 10 7 131047-362 602 14 2 847(133-3924) 0.006* Log addit			AA	10	7	1.40 (0.50–3.90)	0.522	14	2	7.94 (1.69–37.21)	0.009*
Recession GA-AA 68 56 1/2 (6 080-1.98) 0.317 50 52 1.1 (1066-1.83) 0.7 (1) Recession GG-AA 176 168 1 12		Dominant	GG	118	119	1		74	82	1	
Recessive Ge-GA 16 16 1			GA-AA	68	56	1.26 (0.80–1.98)	0.317	50	52	1.1 (0.66–1.83)	0.726
NAM NAM <td></td> <td>Recessive</td> <td>GG-GA</td> <td>176</td> <td>168</td> <td>1</td> <td></td> <td>110</td> <td>132</td> <td>1</td> <td></td>		Recessive	GG-GA	176	168	1		110	132	1	
Log-additive (15'81'9544)12'10'83-17'10.31113'8 (0.91-2.1)0.314LUNC0824 (15'81'9544)Alle (16'8')A278111 </td <td rowspan="2"></td> <td></td> <td>AA</td> <td>10</td> <td>7</td> <td>1.31 (0.47–3.62)</td> <td>0.602</td> <td>14</td> <td>2</td> <td>8.47 (1.83–39.24)</td> <td>0.006*</td>			AA	10	7	1.31 (0.47–3.62)	0.602	14	2	8.47 (1.83–39.24)	0.006*
LINCOM24 (\$78)15944 Allele A P <td>Log-additive</td> <td></td> <td></td> <td></td> <td>1.21 (0.83–1.76)</td> <td>0.311</td> <td></td> <td></td> <td>1.38 (0.91–2.11)</td> <td>0.134</td>		Log-additive				1.21 (0.83–1.76)	0.311			1.38 (0.91–2.11)	0.134
rs781994 G G 98 17 0.71 (0.51-0.97) 0.034* 69 73 1.03 (0.70-1.51) 0.892 Genotype AA 99 82 1 63 75 1.02 (0.60-1.72) 0.513 GG 97 0.30 (0.70-2.61) 0.633 4.70 51 1.02 (0.60-1.72) 0.513 Dominant AA 99 82 0.21 (0.2-0.63) 0.05 75 1.03 (0.40-2.61) 0.53 AG-GG 99 82 0.75 (0.49-1.16) 0.133 58 62 1.02 (0.62-1.67) 0.943 Recessive AA-GG 99 82 1.1 0.013-0.70 0.023 1.02 (0.41-2.53) 0.941 Genotype A N 1.53 1.6 (0.11-0.70) 0.023 1.1 1.02 (0.62-1.67) 0.941 Genotype A N 77 1.03 (0.40-2.61) 0.921 1.1 1.02 (0.62-1.67) 0.941 Genotype A N 78 1.1 1.2 1.1 1.02 (0.62-1.67) 0.941 F239207 Alle A 74 1.2 1.1 1.1 1.1 1.1 1.2 1.1 F239207 G G 1.7 <	LINC00824	Allele	А	278	235	1		185	201	1	
Genotype AA 99 82 1 69 75 1 1 AG 80 71 090107-08 063 47 51 120 (00-172) 0.91 Dominatt AG 92 020 (01-060) 000 10 10 100 (00-172) 0.91 Dominatt AA 92 020 (01-060) 0.91 58 62 120 (00-172) 0.93 Recessive AA-AG 17 153 1 1 16 120 (00-172) 0.93 Log-additive - Mac 179 153 1 1 161 120 (00-172) 0.93 Genotype Alele - Mac 170 131 121 120 (00-172) 0.93 Its29307 Alele G 367 379 1 111 122 140 (00-172) 0.93 Its29307 AG 17 7 120 (00-172) 160 (01-12) 0.93 160 120 (00-51-18) <td< td=""><td rowspan="5">rs7815944</td><td></td><td>G</td><td>98</td><td>117</td><td>0.71 (0.51–0.97)</td><td>0.034*</td><td>69</td><td>73</td><td>1.03 (0.70-1.51)</td><td>0.892</td></td<>	rs7815944		G	98	117	0.71 (0.51–0.97)	0.034*	69	73	1.03 (0.70-1.51)	0.892
AG 80 71 900(57-12) 0.653 97 51 10.2 (0.0-1.72) 0.91 GG 9 23 0.29 (0.12-0.68) 0.005* 11 11 13 (0.40-2.61) 0.96 Dominar AGG 90 82 1 600 90 82 Recessive AAAG 179 153 1 69 58 62 10.2 (0.62-1.67) 0.96 Genessive AAAG 179 153 1 160 160 1 Genessive AAAG 179 153 0.30(13-07) 0.005* 11 11 10.2 (0.41-2.53) 0.96 Commant GG 9 33 1 1 150 120 (0.61-1.63) 0.02 Commant Ga 367 370 1 1 1 1 1 Commant Ga 370 97 0.80 (0.61-16) 0.26 350 26.0 1 1202010 Ga 170 </td <td>Genotype</td> <td>AA</td> <td>99</td> <td>82</td> <td>1</td> <td></td> <td>69</td> <td>75</td> <td>1</td> <td></td>		Genotype	AA	99	82	1		69	75	1	
Image GG 9 23 0.29(1)(2-0.68) 0.00* 11 11 1.01 0.03(0.4-0.61) 0.91 Dominant AA 99 82 1 60 75 1 1 Recessive AAA 179 120 175(0.49-1.61) 58 58 102 102(0.62-1.67) 0.91 Gender			AG	80	71	0.90 (0.57-1.42)	0.653	47	51	1.02 (0.60-1.72)	0.951
Image AA 99 82 1 93 93 1 93 93 1 93<			GG	9	23	0.29 (0.12-0.68)	0.005*	11	11	1.03 (0.40-2.61)	0.956
Recessive AG-GG 89 94 0.75 (0.49-1.10) 0.13 81 12 1.02 (0.2-1.7) 0.93 Recessive AA-AG 19 13 1 10 16 16 12 12 0.93 Incomplex Incomplex Incomplex Incomplex Incomplex Incomplex 102 (0.1-2.5) 0.94 Conder Incomplex Male Incomplex		Dominant	AA	99	82	1		69	75	1	
RecessiveAA-AG17913311161161161161162161161162161161162161 <t< td=""><td></td><td></td><td>AG-GG</td><td>89</td><td>94</td><td>0.75 (0.49–1.16)</td><td>0.193</td><td>58</td><td>62</td><td>1.02 (0.62-1.67)</td><td>0.943</td></t<>			AG-GG	89	94	0.75 (0.49–1.16)	0.193	58	62	1.02 (0.62-1.67)	0.943
Index		Recessive	AA-AG	179	153	1		116	126	1	
IndependentIndepende			GG	9	23	0.30 (0.13–0.70)	0.005*	11	11	1.02 (0.41-2.53)	0.966
GenderMaleFemaleLINC01414 r298207AlleleG36737911111221RA107911.21 (0.89-1.6.6)0.264352601.48 (0.84-2.6.1)0.176GenotypeGG1471511521221.06 (0.51-2.1.8)0.878A73770.88 (0.66-1.4.6)0.93221203.99 (0.77-20.64)0.991DominantGG1772.53 (1.02-6.28)0.046*723.99 (0.77-20.64)0.992RecessiveGA-AA90841.11 (0.76-1.62)0.64*723.92 (0.77-20.00)0.101AAA1772.54 (1.03-6.26)0.043*72.92 (0.27-20.00)0.101LINC00824 r7815944AlleleA16110.75 (0.56-1.00)0.2111LINC00824 r7815944AlleleA3623311111LINC00824 		Log-additive	_			0.68 (0.48–0.95)	0.023*			1.02 (0.69–1.49)	0.941
LINC0141 r298207AlleleGG3673791I11112211r298207AA107911.21(0.89-1.60)0.22635261.48(0.84-2.61)0.176GenotypeGG1471511-455010.876AA70.98(0.66-1.40)0.9322123.99(0.77-20.64)0.997DominantGG14715114513.993.99(0.77-20.64)0.993RecessiveGG-GA1202.811.11(0.76-1.62)0.68228241.29(0.66-2.55)0.456RecessiveGG-GA2.022.811.11(0.76-1.62)0.643*72.99(0.77-20.00)0.161LINC00824AGG-GA2.022.811.11(0.76-1.62)0.643*73.92(0.77-20.00)0.161LINC00824AGG-GA2.022.841.61(0.76-1.62)0.643*71.41(0.71-2.61)0.216LINC00824AlleleA3.623.311-1.41 <td>Gender</td> <td></td> <td></td> <td>Male</td> <td></td> <td></td> <td></td> <td>Female</td> <td>2</td> <td></td> <td></td>	Gender			Male				Female	2		
rs298207A107911.21 (0.89-1.66)0.22635261.48 (0.84-2.61)0.17GenotypeGG1471511535010.87AA73740.98 (0.66-1.46)0.93221221.06 (0.51-2.18)0.87DominantGG14772.53 (1.02-6.28)0.046*723.99 (0.77-20.64)0.99DominantGG14715115511.20 (0.65-2.51)0.456RecessiveGG-GA202815671.20 (0.65-2.51)0.456RecessiveGG-GA20281-671.20 (0.67-2.50)0.457LINC00824GG-GA20281-671.40 (0.72-20.00)0.101LINC00824AleleA323311-83.90 (0.77-20.00)0.101LINC00824AleleA3623311-1011.80 (0.67-1.75)0.761ST815944AleleA161410.75 (0.56-1.00)0.52551491.80 (0.67-1.75)0.761LINC00824AleleAA1341181343134 <t< td=""><td>LINC01414</td><td>Allele</td><td>G</td><td>367</td><td>379</td><td>1</td><td></td><td>111</td><td>122</td><td>1</td><td></td></t<>	LINC01414	Allele	G	367	379	1		111	122	1	
RenotypeGG1471511145501GA73700.98 (0.61-4.6)0.93221221.66 (0.51-2.18)0.878AA72.53 (1.02-6.28)0.046*72390 (0.72-0.64)0.909DominantGG147151145501ACA90841.11 (0.76-1.62)0.58228241.29 (0.62-2.51)0.456RecessiveGG-GA2028166721.20 (0.62-2.51)0.101LIOCOR24GG-GA1772.54 (1.03-6.26)0.043*72320 (0.77-20.00)0.101LIOCOR24GG-GA2.022.851.611111.10 <td>rs298207</td> <td></td> <td>A</td> <td>107</td> <td>91</td> <td>1.21 (0.89–1.66)</td> <td>0.226</td> <td>35</td> <td>26</td> <td>1.48 (0.84–2.61)</td> <td>0.176</td>	rs298207		A	107	91	1.21 (0.89–1.66)	0.226	35	26	1.48 (0.84–2.61)	0.176
Recessive GA 73 77 0,98,066-1,40 0,932 21 22 1,06,051-2,18 0,037 Dominant GA 17 7 2,53,10,2-6,28 0,046* 7 2 3,90,07,2-0,64 0,09 Dominant GG 147 151 1 552 56 1 1,20,066-2,55 0,456 Recessive GG-GA 20 28 1,110,76-1,62 0,582 28 24 1,20,066-2,55 0,456 Recessive GG-GA 20 28 1 56 72 1 1 1 LINC00824 GG-GA 17 7 254(1,03-6,26) 0,43* 7 2 3,90,077-20,00 0,101 LINC00824 GG - 122(0,89-1,61) 0,43* 7 143 (0,82-2,46) 0,204 S7815944 Allele A 32 314 1 1 1 1 0,30,05-1,10 0,101 34 32 1 1 1		Genotype	GG	147	151	1		45	50	1	
NominateAA177253(1.02-6.28)0.046*723.99(0.77-20.64)0.099DominateGG1471510145050111AR2081GG-GA20841.11 (0.76-1.62)0.58228241.29 (0.66-2.55)0.456RecessiveGG-GA202816672111LINC00824GG-GA2028172.0 (0.77-20.00)0.101LINC00824Allele-122 (0.89-1.66)0.043*72.0 (0.77-20.00)0.101LINC00824AlleleA3623311111.43 (0.82-2.46)0.204RecessiveAllele1661410.75 (0.56-1.00)0.5251491.88 (0.67-1.75)0.746GenotypeAA13411811343911332DominantAG134184141.81343911332DominantAA1341841.4134391134391134391134314<			GA	73	77	0.98 (0.66–1.46)	0.932	21	22	1.06 (0.51-2.18)	0.878
Image: height base in the section of the section o			AA	17	7	2.53 (1.02–6.28)	0.046*	7	2	3.99 (0.77–20.64)	0.099
RecessiveGA-AA90841.11 (0.76-1.62)0.58228241.29 (0.66-2.55)0.456RecessiveGG-GA202281667211Log-additive-122 (0.89-1.66)0.043*723.92 (0.77-20.00)0.101LINC00824AlleleA3623111011051143 (0.82-2.46)0.204LINC00824AlleleA362311101101108 (0.67-1.75)0.764GenotypeAA141410.75 (0.56-1.00)0.05251491.08 (0.67-1.75)0.746GenotypeAA13418411343911GominantAA13418134343911AcGG105180.78 (0.59-1.26)0.028*9110.94 (0.35-2.58)0.912DominantAAA1341813434341343		Dominant	GG	147	151	1		45	50	1	
RecessiveGG-GA2028166721 AA 177254 (1.03-6.26) 0.043* 72392 (0.77-20.00)0.101 $Log-additive$ -1.22 (0.89-1.66)0.2181.43 (0.82-2.46)0.204 $LINC00824$ AlleleA36233111051 $r57815944$ AlleleA3623111311011051 $Genotype$ AA1460.75 (0.56-1.00)0.05251491.08 (0.67-1.75)0.746 $Genotype$ AA134118134391332 GG 11230.43 (0.20-0.91)0.028*9110.94 (0.35-2.58)0.912 $Dominant$ AA13411813439133234 $Recessive$ AA-AG2821311734381.28 (0.67-2.43)0.457 Gg 11230.45 (0.22-0.96)0.037*9110.81 (0.31-2.08)0.655 $Log-additive$ $-$ 11230.45 (0.22-0.96)0.037*9110.81 (0.31-2.08)0.655			GA-AA	90	84	1.11 (0.76–1.62)	0.582	28	24	1.29 (0.66–2.55)	0.456
AA1772.54 (1.03-6.26) 0.043^* 72 $3.92 (0.77-20.00)$ 0.101 LOg-additive1.22 (0.89-1.66) 0.218 - $1.43 (0.82-2.46)$ 0.204 LINC00824 Ts7815944AlleleA362 331 1 1.5 1.61 $1.60 (0.51-0.00)$ 0.52 51 49 $1.08 (0.67-1.75)$ 0.746 GenotypeAA141 $0.75 (0.56-1.00)$ 0.52 51 49 $1.08 (0.67-1.75)$ 0.746 GenotypeAA144 18 1 1 34 39 1 1 GenotypeAA 94 95 $0.87 (0.59-1.26)$ 0.454 33 27 $1.41 (0.71-2.81)$ 0.332 DominantAA 14 18 1 1 34 39 1 1 AG-GG 15 18 $0.78 (0.59-1.26)$ 0.179 42 38 $1.28 (0.67-2.43)$ 0.457 RecessiveAA-AG 28 213 1 1 10 11 $0.81 (0.31-2.08)$ 0.655 Log-additive $ 1$ 23 $0.55 (0.56-1.00)$ 0.52 11 $0.80 (0.8-1.71)$ 0.753		Recessive	GG-GA	220	228	1		66	72	1	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			AA	17	7	2.54 (1.03–6.26)	0.043*	7	2	3.92 (0.77–20.00)	0.101
LINCC00824 rs7815944 Allele A 362 331 1 101 105 1 rs7815944 G 116 141 0.75 (0.56-1.00) 0.052 51 49 1.08 (0.67-1.75) 0.746 Genotype AA 134 118 1 34 39 1 AG 94 95 0.87 (0.59-1.26) 0.454 33 27 1.41 (0.71-2.81) 0.332 GG 11 23 0.43 (0.20-0.91) 0.028* 9 11 0.94 (0.35-2.58) 0.912 Dominant AA 134 118 1 34 39 1 Recessive AA-AG 134 118 1 34 39 1 Log-additive - 134 18 1 34 39 1 Log-additive AA-AG 28 213 1 34 39 1 128 (0.67-2.43) 0.457 Log-additive - GG 11 23 0.45 (0.22-0.96) 0.037* 9 11 0.81 (0.31-2.08) 0.655		Log-additive	_			1.22 (0.89–1.66)	0.218			1.43 (0.82–2.46)	0.204
rs7815944 G 116 141 0.75 (0.56-1.00) 0.052 51 49 1.08 (0.67-1.75) 0.746 Genotype AA 134 118 1 34 39 1 332 AG 94 95 0.87 (0.59-1.26) 0.454 33 27 1.41 (0.71-2.81) 0.332 GG 11 23 0.43 (0.20-0.91) 0.028* 9 11 0.94 (0.35-2.58) 0.912 Dominant AA 134 118 1 34 39 1 Recessive AA-AG 134 118 1 34 39 1 Ma-GG 105 118 0.78 (0.54-1.12) 0.179 42 38 1.28 (0.67-2.43) 0.457 Recessive AA-AG 28 213 1 67 66 1 Log-additive - 0.75 (0.56-1.00) 0.052 11 0.80 (0.68-1.71) 0.655	LINC00824	Allele	А	362	331	1		101	105	1	
Genotype AA 134 118 1 34 39 1 AG 94 95 0.87 (0.59-1.26) 0.454 33 27 1.41 (0.71-2.81) 0.332 GG 11 23 0.43 (0.20-0.91) 0.028* 9 11 0.94 (0.35-2.58) 0.912 Dominant AA 134 118 1 34 39 1 AG-GG 105 118 0.78 (0.54-1.12) 0.179 42 38 1.28 (0.67-2.43) 0.457 Recessive AA-AG 228 213 1 67 66 1 GG 11 23 0.45 (0.22-0.96) 0.037* 9 11 0.81 (0.31-2.08) 0.655 Log-additive - - 0.75 (0.56-1.00) 0.052 1.18 0.75 (0.56-1.00) 0.55 1.08 (0.68-1.71) 0.753	rs7815944		G	116	141	0.75 (0.56–1.00)	0.052	51	49	1.08 (0.67-1.75)	0.746
AG 94 95 0.87 (0.59-1.26) 0.454 33 27 1.41 (0.71-2.81) 0.332 GG 11 23 0.43 (0.20-0.91) 0.028* 9 11 0.94 (0.35-2.58) 0.912 Dominant AA 134 118 1 34 39 1 AG-GG 105 118 0.78 (0.54-1.12) 0.179 42 38 1.28 (0.67-2.43) 0.457 Recessive AA-AG 228 213 1 67 66 1 655 Log-additive - - 0.75 (0.56-1.00) 0.052 11 0.81 (0.31-2.08) 0.655		Genotype	AA	134	118	1		34	39	1	
GG 11 23 0.43 (0.20-0.91) 0.028* 9 11 0.94 (0.35-2.58) 0.912 Dominant AA 134 118 1 34 39 1 AG-GG 105 118 0.78 (0.54-1.12) 0.179 42 38 1.28 (0.67-2.43) 0.457 Recessive AA-AG 228 213 1 67 66 1 GG 11 23 0.45 (0.22-0.96) 0.037* 9 11 0.81 (0.31-2.08) 0.655 Log-additive - - 0.75 (0.56-1.00) 0.052 1.08 (0.68-1.71) 0.753			AG	94	95	0.87 (0.59–1.26)	0.454	33	27	1.41 (0.71–2.81)	0.332
Dominant AA 134 118 1 34 39 1 AG-GG 105 118 0.78 (0.54–1.12) 0.179 42 38 1.28 (0.67–2.43) 0.457 Recessive AA-AG 228 213 1 67 66 1 GG 11 23 0.45 (0.22–0.96) 0.037* 9 11 0.81 (0.31–2.08) 0.655 Log-additive - - 0.75 (0.56–1.00) 0.052 1.08 (0.68–1.71) 0.753			GG	11	23	0.43 (0.20-0.91)	0.028*	9	11	0.94 (0.35–2.58)	0.912
AG-GG 105 118 0.78 (0.54–1.12) 0.179 42 38 1.28 (0.67–2.43) 0.457 Recessive AA-AG 228 213 1 67 66 1 GG 11 23 0.45 (0.22–0.96) 0.037* 9 11 0.81 (0.31–2.08) 0.655 Log-additive - 575 (0.56–1.00) 0.052 1.08 (0.68–1.71) 0.753		Dominant	AA	134	118	1		34	39	1	
Recessive AA-AG 228 213 1 67 66 1 GG 11 23 0.45 (0.22–0.96) 0.037* 9 11 0.81 (0.31–2.08) 0.655 Log-additive - 0.75 (0.56–1.00) 0.052 1.08 (0.68–1.71) 0.753			AG-GG	105	118	0.78 (0.54–1.12)	0.179	42	38	1.28 (0.67–2.43)	0.457
GG 11 23 0.45 (0.22-0.96) 0.037* 9 11 0.81 (0.31-2.08) 0.655 Log-additive - 0.75 (0.56-1.00) 0.052 1.08 (0.68-1.71) 0.753		Recessive	AA-AG	228	213	1		67	66	1	
Log-additive – 0.75 (0.56–1.00) 0.052 1.08 (0.68–1.71) 0.753			GG	11	23	0.45 (0.22-0.96)	0.037*	9	11	0.81 (0.31-2.08)	0.655
		Log-additive	-			0.75 (0.56–1.00)	0.052			1.08 (0.68–1.71)	0.753

Table 4 (continued)

p values were calculated by logistic regression analysis adjusted by age and gender

Bold indicate that p < 0.05 means the data is statistically significant

COPD chronic obstructive pulmonary disease, SNP single nucleotide polymorphism, OR odds ratio, 95% CI 95% confidence interval

genotyping. Primer design (Additional file 1: Table S1) and data management are performed based on corresponding supporting software. About 10% of subjects were repeatedly genotyped for quality control, and the results were consistent.

Statistical analysis

Sample *t* test or χ^2 test were used to evaluated the distribution of age and gender between COPD patients and healthy controls. HWE of selected SNPs in controls was detected by a goodness-of-fit χ^2 test. Logistic analysis adjusted by age and gender were applied to estimate the genetic contribution of selected SNPs to COPD susceptibility by calculating odds ratios (OR) and 95% confidence intervals (CI). Multifactor dimensionality reduction (MDR) analysis was used for analyze gene-gene interaction. Analysis of Variance (ANOVA) was used to evaluate the association between genotypes of *LINC01414/LINC00824* variants and clinical characteristics of COPD patients. Data analyses were conducted using SPSS 20.0, PLINK 1.0.7, and MDR software. A *p* value < 0.05 was defined as statistical significance.

Results

Participant characteristics.

The participants consisted of 315 cases (239 males and 76 females, 71.9 ± 10.1 years) and 314 controls (237 males and 77 females, 71.2 ± 6.8 years). Table 1 summarized the features of participants, including age, gender, smoking, body mass index (BMI), complication, clinical symptoms (wheezing, dyspnea, chest distress), respiratory rate, pulse rate, forced vital capacity (FVC), forced the first second of expiratory volume (FEV1) and FEV1/FVC. No statistically significant difference in age (p=0.307) and gender (p=0.926) distribution was found.

Correlation of selected polymorphisms with COPD risk

Three SNPs (rs6994670 and rs298207 in *LINC01414*, rs7815944 in *LINC00824*) of the controls were consistent with HWE. The MAF of all the SNPs in this group were > 5% (Table 2). The prevalence of *LINC01414* rs6994670 G-allele frequencies was lower in COPD patients than in controls (OR = 0.73, 95% CI 0.56–0.94, p = 0.015).

The genetic polymorphisms of selected SNPs were related to COPD susceptibility, as shown in Table 3. Rs699467 in *LINC01414* might be a protective factor for

COPD occurrence under the dominant (OR = 0.71, 95% CI 0.51–0.97, p = 0.034) and additive (OR = 0.73, 95% CI 0.56–0.95, p = 0.018) models. For *LINC01414* rs298207, AA genotype was seen more frequent in COPD-patients compared with GG (OR = 2.87, 95% CI 1.30–6.36, p = 0.009) or GG-GA (OR = 2.88, 95% CI 1.31–6.31, p = 0.008) genotype. Carriers of GG genotype of rs7815944 in *LINC00824* had a lower frequent in COPD-patients compared with AA genotype (OR = 0.55, 95% CI 0.30–0.99, p = 0.047) and AA-AG genotype (OR = 0.56, 95% CI 0.31–0.99, p = 0.046).

Stratification analysis for the genetic correlation by age, gender and smoking

We also evaluated the contribution of confounding factors (age, gender and smoking status) to the genetic relationship between selected polymorphisms and COPD risk, as listed in Tables 4 and 5. When stratified analysis by age (Table 4), rs7815944 was associated with a reduced COPD risk under the allele (OR=0.71, p=0.034), genotype (OR = 0.29, p = 0.005), recessive (OR = 0.30, p=0.005) and additive (OR=0.68, p=0.023) models in the subjects aged>70 years. Rs6994670 was observed to reduce the risk of COPD in the allele (OR = 0.61, p = 0.012), genotype (OR = 0.57, p = 0.037;and OR = 0.33, p = 0.031), dominant (OR = 0.52, p = 0.012) and additive (OR=0.57, p=0.007) models among the subjects with age \leq 70 years. Rs298207 seem associated to development of COPD (OR=7.94, p=0.009; and OR = 8.47, p = 0.006) at age ≤ 70 years.

In the stratified analysis by gender (Table 4), rs298207 and rs7815944 variants contributed to COPD risk in males. In which, rs298207-AA genotype was seen more frequent in COPD-patients compared with GG (OR=2.53, p=0.046) or GG-GA (OR=2.54, p=0.043) genotype among males. Rs7815944 was a protective factor for COPD susceptibility (OR=0.43, p=0.028; and OR=0.45, p=0.037) in males.

Stratified analysis by smoking status (Table 5), we found that rs7815944 was associated with a reduced susceptibility of COPD in the allele (OR=0.45, p=0.040), genotype (OR=0.17, p=0.044), recessive (OR=0.16, p=0.031) models among former smokers. However, no significant association of these SNPs with COPD risk in current smokers and never smokers was found.

Table 5 🛛	ssociation betw	veen polymorp	ohisms ar	nd COPD ris	sk stratified by sm	oking								
SNP ID	Model	Genotype	Case	Control	OR (95%CI)	٩	Case	Control	OR (95%CI)	٩	Case	Control	OR (95%CI)	d
Smoking			Current				Former				Never			
LINC00824	Allele	A	123	47	-		97	21	-		239	178	1	
rs7815944		U	43	21	0.78 (0.42–1.45)	0.438	31	15	0.45 (0.21–0.97)	0.040*	93	58	1.19 (0.82–1.75)	0.361
	Genotype	AA	43	16	-		36	8	-		87	65	1	
		AG	37	15	0.93 (0.40–2.15)	0.867	25	5	1.08 (0.30–3.94)	0.906	65	48	0.99 (0.6–1.62)	0.966
		99	c	°.	0.36 (0.06–2.02)	0.246	ŝ	5	0.17 (0.03–0.96)	0.044*	14	5	1.96 (0.66–5.76)	0.223
	Dominant	AA	43	16	-		36	œ	-		87	65	-	
		AG-GG	40	18	0.83 (0.37–1.85)	0.647	28	10	0.68 (0.21–2.14)	0.506	79	53	1.08 (0.67–1.74)	0.751
	Recessive	AA-AG	80	31	-		61	13	—		152	113	-	
		99	ŝ	°	0.37 (0.07–2.01)	0.250	ŝ	5	0.16 (0.03–0.84)	0.031*	14	5	1.97 (0.68–5.66)	0.211
	Log-additive	I			0.76 (0.39–1.48)	0.413			0.52 (0.22–1.20)	0.124			1.17 (0.79–1.72)	0.443
<i>p</i> values were Bold indicate	e calculated by logi: that <i>p</i> < 0.05 mean:	stic regression and s the data is statis	alysis adjus tically sign	ted by age an ificant	d gender									
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COPD chronic obstructive pulmonary disease, SNP single nucleotide polymorphism, OR odds ratio, 95% Cl 95% confidence interval

SNP ID	Model	Genotype	COPD	with dy	spnea		COPD	with wh	eezing	
			Yes	No	OR (95%CI)	р	Yes	No	OR (95%CI)	p
LINC01414	Allele	G	180	242	1		239	179	1	
rs298207		А	48	82	0.79 (0.52–1.18)	0.246	65	59	0.83 (0.55–1.23)	0.349
	Genotype	GG	76	90	1		94	71	1	
		GA	28	62	0.50 (0.29–0.88)	0.016*	51	37	1.03 (0.60–1.74)	0.925
		AA	10	10	0.91 (0.34-2.45)	0.852	7	11	0.40 (0.14-1.13)	0.083
	Dominant	GG	76	90	1		94	71	1	
		GA-AA	38	72	0.56 (0.33-0.94)	0.029*	58	48	0.88 (0.54–1.45)	0.615
	Recessive	GG-GA	104	152	1		145	108	1	
		AA	10	10	1.16 (0.44–3.05)	0.768	7	11	0.40 (0.14–1.10)	0.075
	Log-additive	-			0.72 (0.47-1.08)	0.110			0.80 (0.54–1.18)	0.260
LINC00824	Allele	А	170	242	1		237	169	1	
rs7815944		G	60	90	0.95 (0.65–1.39)	0.788	69	77	0.64 (0.44–0.93)	0.021*
	Genotype	AA	62	87	1		89	58	1	
		AG	46	68	0.95 (0.57–1.59)	0.843	59	53	0.72 (0.44–1.20)	0.209
		GG	7	11	0.61 (0.21-1.75)	0.358	5	12	0.22 (0.07–0.67)	0.008*
	Dominant	AA	62	87	1		89	58	1	
		AG-GG	53	79	0.89 (0.55–1.47)	0.660	64	65	0.63 (0.39–1.02)	0.059
	Recessive	AA-AG	108	155	1		148	111	1	
		GG	7	11	0.63 (0.22–1.74)	0.369	5	12	0.25 (0.08–0.76)	0.014*
	Log-additive	_			0.86 (0.58–1.29)	0.472			0.59 (0.40–0.89)	0.011*

 Table 6
 Association of polymorphisms with dyspnea and wheezing in COPD patients

p values were calculated by logistic regression analysis adjusted by age and gender

Bold indicate that p < 0.05 means the data is statistically significant

COPD chronic obstructive pulmonary disease, SNP single nucleotide polymorphism, OR odds ratio, 95% CI 95% confidence interval

Correlation of selected polymorphisms with clinical symptoms in COPD patients

The correlation of selected polymorphisms with clinical symptoms in COPD patients was also assessed, and the results was shown in Table 6. We found the association between rs298207 genotype and COPD patients with dyspnea (OR=0.50, p=0.016; and OR=0.56, p=0.029). Moreover, our result displayed that rs7815944 was related to COPD patients with wheezing under the allele (OR=0.64, p=0.021), genotype (OR=0.22, p=0.008), recessive (OR=0.25, p=0.014) and additive (OR=0.59, p=0.011) models.

MDR analysis for gene-gene interaction

MDR analysis was analyzed to evaluate the contribution of gene–gene interaction to COPD risk. Figure 1 revealed the additive effect between *LINC01414* rs6994670-GG, *LINC01414* rs298207-AA, *LINC00824* rs7815944-GG towards COPD susceptibility. The interactions of these SNPs was displayed as the dendrogram

and Fruchterman-Reingold (Fig. 2). Our results demonstrated that *LINC01414* rs6994670 was the best onefactor model for COPD risk (testing accuracy=0.5468, CVC=10/10, p=0.0188, Table 7). Furthermore, the twofactor model (*LINC01414* rs6994670 and *LINC00824* rs7815944) was found to be the best multi-loci model for COPD risk (testing accuracy=0.5518, CVC=10/10, p=0.0037).

The association between selected variants and clinical characteristics of COPD patients

The association between *LINC01414/ LINC00824* SNPs and clinical indicators in COPD patients was assessed, as displayed in Table 8. We found that the genotypes of *LINC00824* rs7815944 was associated with respiratory rate of COPD patients (p=0.022). However, no statistically association was observed on rs6994670 and rs298207 in *LINC01414*.



Discussion

In our study, rs699467 in *LINC01414* and rs7815944 in *LINC00824* might be protective factors for COPD occurrence, while *LINC01414* rs298207 was associated with the increased risk of COPD in the whole population. Specially, age, gender, and smoking status might contributed to the association of these polymorphisms with COPD risk. Moreover, we found the association between rs298207 genotype and COPD patients with dyspnea, and rs7815944 was related to COPD patients with wheezing. Our findings firstly indicated that



Table 7 MDR analysis of gene-gene interaction for COPD risk

Model	Training Bal. Acc	Testing Bal. Acc	cvc	р
LINC01414 rs6994670	0.5468	0.5468	10/10	0.0188
LINC01414 rs6994670, LINC00824 rs7815944	0.5591	0.5518	10/10	0.0037
LINC01414 rs6994670, LINC01414 rs298207, LINC00824 rs7815944	0.5688	0.508	10/10	0.0012

p values were calculated using χ^2 tests

Bold indicate that p < 0.05 indicates statistical significance

MDR multifactor dimensionality reduction, Bal. Acc. balanced accuracy, CVC cross-validation consistency, OR odds ratio, CI confidence interval

Table 8 Association of clinical characteristics with genotypes of candidate SNPs among COPD patients

Variables	LINC01414 rs6994670	0				
	AA	AG	GG	р		
Respiratory rate, times/min	22.24 ± 2.35	22.49 ± 2.73	21.70±1.57	0.519		
Pulse rate, times/min	86.50 ± 11.07	86.86 ± 12.81	78.20 ± 7.63	0.078		
FVC, L	2.01 ± 0.71	1.90 ± 0.66	2.03 ± 0.42	0.665		
FEV1, L	1.23 ± 0.57	1.20 ± 0.68	1.20 ± 0.41	0.932		
FEV1/FVC, %	52.18 ± 11.83	48.55 ± 11.23	57.65 ± 13.46	0.133		
Variables	LINC01414 rs298207					
	AA	GA	GG	р		
Respiratory rate, times/min	22.15 ± 2.94	22.29 ± 2.43	22.37 ± 2.46	0.914		
Pulse rate, times/min	85.05 ± 13.57	87.86±12.44	85.81 ± 11.12	0.357		
FVC, L	2.00 ± 0.64	1.89 ± 0.56	2.02 ± 0.75	0.555		
FEV1, L	1.28 ± 0.54	1.13 ± 0.48	1.27 ± 0.67	0.384		
FEV1/FVC, %	5086 ± 15.95	53.44 ± 210.66	50.27 ± 11.99	0.387		
Variables	LINC00824 rs7815944					
	AA	AG	GG	р		
Respiratory rate, times/min	22.36 ± 2.5	22.48 ± 2.49	20.78±1.26	0.022		
Pulse rate, times/min	86.22 ± 11.12	86.32 ± 12.28	87.28 ± 12.86	0.937		
FVC, L	1.98 ± 0.61	2.00 ± 0.76	1.84 ± 0.77	0.777		
FEV1, L	1.19 ± 0.52	1.22 ± 0.65	1.41 ± 0.81	0.489		
FEV1/FVC, %	52.35 ± 11.23	50.34 ± 12.04	50.46 ± 16.01	0.657		

p values were calculated by Analysis of Variance (ANOVA)

Bold indicate that p < 0.05 indicates statistical significance

COPD chronic obstructive pulmonary disease, BMI body mass index, FVC including forced vital capacity, FEV1 forced the first second of expiratory volume

LINC01414/LINC00824 polymorphisms might play a role in the occurrence of COPD.

LINC01414, located at chromosome 8q12.3, is a long intergenic non-protein coding RNA 1414. The function of LINC01414 has not been reported. LINC00824, located at chromosome 8q24.21, is also known as LINC01263. Genome-wide association studies reported that *LINC00824* polymorphisms were associated with primary spontaneous pneumothorax and rheumatoid arthritis [18, 19]. Here, we firstly found that rs699467 in *LINC01414* and rs7815944 in *LINC00824* might be protective factors for COPD occurrence, while *LINC01414* rs298207 increased the risk of COPD in the whole population.

The occurrence of COPD is caused by combined effects of genetic background, gender, smoking and an aging population [20]. COPD is the leading causes of disability and death in older people, and significant sex difference can be observed, especially deaths in older men [21]. We also evaluated the contribution of confounding factors

(age and gender) to the genetic relationship between selected polymorphisms and COPD risk. Stratified analysis by age, rs7815944 was related to a reduced COPD risk in the subjects aged > 70 years. Rs6994670 was associated with the reduced risk of COPD, while rs298207 might have a higher susceptibility to COPD at age \leq 70 years. In the stratified analysis by gender, rs298207 and rs7815944 variants were correlated with COPD risk in males. Our results suggested that the genetic contribution of LINC01414/LINC00824 variants to COPD risk was gender- and age-specific. It is generally believed that smoking is the main risk factor for COPD development [22]. Previously, LINC00824 was higher expression in current smokers compared with former smokers [16]. Stratified analysis by smoking status, we found that rs7815944 was associated with the reduced susceptibility of COPD in former smokers but not current smokers. These hinted that LINC00824 might have an important role in the COPD pathogenesis. The potential function of rs7815944 is unknown. We speculate that the biological function of rs7815944 may be involved in affecting the expression of I LINC00824, which needed to be further studied.

Several limitations in our study is unavoidable. First, the participants were Chinese Han population from a single center (the same hospital), therefore, the selection bias was inevitable and our results are not representative of other ethnic groups. Second, we only analyzed three SNPs in the *LINC01414/LINC00824* gene, and other polymorphisms and other lncRNA genes were not considered. Third, the functional effects of *LINC01414/LINC00824* variants in the pathogenesis of COPD were not explored.

Conclusion

In summary, we found that *LINC01414* rs699467 and *LINC00824* rs7815944 were associated with lower prevalence of COPD, while *LINC01414* rs298207 was associated with the increased risk of COPD in the Chinese Han population. Our finding provided further insights into *LINC01414/LINC00824* polymorphisms at risk of COPD occurrence and accumulated evidence for the genetic susceptibility of COPD.

Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1186/s12890-021-01579-3.

Additional file 1. Primers sequence.

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Authors' contributions

XZ and YZ: drafted the work or revised it critically for important content; YZ and QL: performed the experiments; ML and YY: analyzed the data; YX: prepared the figures and/or tables; YD: conceived and designed the experiments. All authors have read and approved the manuscript.

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

The study was approved by the medical ethics committee of Hainan General Hospital and was in the Declaration of Helsinki. All the subjects signed a written informed consent.

Consent for publication

Written informed consent was obtained from the patient for publication of this report.

Competing interests

The authors declare that they have no conflict of interests.

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