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Correlation between resistin gene polymorphism and clinical aspects of lung cancer

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Abstract

Lung cancer is one of the most common cancers and is associated with a poor survival rate in the Chinese Han population. Analysis of genetic variants could lead to improvements in prognosis following lung cancer treatment. Resistin (RETN) is an important mediator of metabolic diseases and tumor progression. In this study, we explored the effects of RETN single nucleotide polymorphisms (SNPs) on the susceptibility and clinicopathological characteristics of patients with lung cancer. Four RETN SNPs (rs7408174, rs1862513, rs3745367, and rs3219175) were analyzed using TaqMan SNP genotyping in 371 patients with lung cancer and 451 cancer-free controls. The results showed that the RETN SNP rs3219175 with AG or at least 1 A allele was associated with a higher risk of lung cancer than wild-type (GG) carriers. Moreover, the RETN SNP rs3219175 with AG or AG + AA alleles was associated with a higher risk of distant metastasis than that in patients carrying GG alleles. We also used genotype-tissue expression datasets to compare the correlation of the RETN SNP rs3219175 in lung tissue and whole blood. In conclusion, our study demonstrated, for the first time, that RETN polymorphisms were correlated with lung cancer progression in the Chinese Han population.

Abbreviations: CI = confidence interval, GTEx = genotype-tissue expression, HWE = Hardy–Weinberg equilibrium, NSCLC = non-small-cell lung cancer, OR = odds ratio, PCR = polymerase chain reaction, RETN = resistin, SCLC = small-cell lung cancer, SNP = single nucleotide polymorphisms.

Keywords: lung cancer, polymorphism, resistin

1. Introduction

Lung cancer is one of the most common types of cancer worldwide and is associated with a poor 5-year relative survival rate.[1] The specific mechanisms underlying lung cancer development and progression are still unclear. Although cigarette smoking and alcohol consumption are known to directly induce lung cancer, various other environmental risks, such as exposure to second-hand smoke, air pollution, and genetic susceptibility, are also involved in the development of lung cancer.[2] Indeed, multiple genetic and epigenetic changes have been shown to be associated with lung cancer development.[3] Increased understanding of genetic mechanisms, including heterogeneity and DNA genotyping, is required to improve our ability to predict prognosis of lung cancer.[4] Therefore, exploration of genetic aberrations is necessary for lung cancer prognosis and risk prediction.

Resistin (RETN) is a 12.5-kDa cysteine-rich protein that is constitutively secreted by adipose tissue.[5] RETN has been reported to have function in inflammation and immune responses and to act as a pro-inflammatory mediator.[6] The *RETN* gene, encoding RETN, is localized on chromosome 9, and several single nucleotide polymorphisms (SNPs) have been identified in the *RETN* promoter and 3′-untranslated regions.[7] Several reports have connected genetic variants in RETN with the risk of various diseases, such as diabetes and colorectal cancer.[8,9] A functional *RETN* gene polymorphism at -420 (rs186513) has been shown to increase susceptibility to type 2 diabetes.[10] Another previous study evaluated a functional *RETN* gene polymorphism, rs3219175, but showed that this SNP was not associated with endometrial cancer.[11] Despite these studies, the correlation between *RETN* gene polymorphisms and lung cancer prognosis remains unclear.

Accordingly, in this report, we performed a case–control study to evaluate 4 SNPs in the *RETN* gene in patients with lung cancer.

2. Materials and methods

2.1. Patients and blood samples

We collected 371 blood specimens from the patients who had been diagnosed with lung cancer, including 279 adenocarcinoma

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lung cancer, 56 squamous cell carcinoma, and 36 other types of lung cancer patients, at Dongyang People's Hospital as the case group from 2014 to 2016. For the control group, 451 health participants without any history of cancer were enrolled. All patients and participants provided written informed consent, and this study was approved by the Ethics Committee of Dongyang People's Hospital. The pathological stages of lung cancer in all patients were determined according to their medical records and the Revised International System for Staging Lung Cancer. A standardized questionnaire and electronic medical record system were used to acquire data on age, sex, smoking history, and alcohol consumption.

2.2. Selection of RETN polymorphisms

Three RETN SNPs were selected from a 2-kb region upstream of RETN (rs7408174, rs1862513, and rs3219175), and 1 (rs3745367) was selected from the intron of RETN; all SNPs had minor allele frequencies of greater than 5%. Most RETN SNPs were known to be associated with type 2 diabetes mellitus or breast cancer.[12,13]

2.3. Genomic DNA extraction

Genomic DNA was extracted from peripheral blood leukocytes using a QIAamp DNA blood kit (Qiagen, CA) according to the manufacturer's instructions. Extracted DNA was stored at −20°C and prepared for genotyping by polymerase chain reaction (PCR).

2.4. Genotyping by real-time PCR

Four *RETN* SNP probes were purchased from Thermo Fisher Scientific Inc. (USA), and assessment of allelic discrimination for *RETN* SNPs was conducted using a Roche LightCycler 480 Instrument II (Roche, Mannheim, Germany). Data were further analyzed with LightCycler 480 Software, Version 1.5 (Roche). PCR was carried out in a total volume of 10 μL, containing 20 to 70 ng genomic DNA, 1 U Taqman Genotyping Master Mix (Thermo Fisher, Applied Biosystems, Foster City, CA), and 0.25 μL probes. The sequence of 4 RETN SNP probes was described as follows: rs3745367, CTCCGACTGTCCCCACCTTATCCAC [A/G]GCTCCAAACCCAA; rs7408174, TTTTACCACAAAAAG GCCCGTTGTA[C/T]TGGAAACAAAGAA; rs1862513, CCT GACCAGTCTCTGGACATGAAGA[C/G]GGAGGCCCTGTTG; rs3219175, CTCCAGCCCTTACTGTCTGCTCAGG[A/G]GCTT CCTCTTGGC. The protocol included an initial denaturation step at 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute.

2.5. Statistical analysis

Differences between the 2 groups were considered significant if *P* values were less than .05. Hardy–Weinberg equilibrium (HWE) was assessed using Chi-square goodness-of-fit tests for biallelic markers. Mann–Whitney *U*-tests and Fisher exact tests were used to compare differences in demographic characteristics between healthy controls and patients with lung cancer. The odds ratios (ORs) and 95% confidence intervals (CIs) for associations between genotype frequencies and the risk of lung cancer or clinicopathological characteristics were estimated by multiple logistic regression models, after controlling for other covariates. All data were analyzed using Statistical Analytic System software (v. 9.1, 2005; SAS Institute, Cary, NC).

Table 1

The distributions of demographical characteristics and clinical parameters in 451 controls and 371 patients with lung cancer.

Variable	Controls (N = 451)	Patients (N = 371)	*P*
Age, y	Mean ± S.D.	Mean ± S.D.	
	44.80 ± 17.09	59.89 ± 10.38	<.001*
Gender	n (%)	n (%)	
Male	231 (51.2)	182 (49.1)	
Female	220 (48.8)	189 (50.9)	.537
Cigarette smoking			
No	408 (90.5)	224 (60.4)	
Yes	43 (9.5)	147 (39.6)	<.001*
Alcohol consumption			
No	389 (86.3)	284 (76.5)	
Yes	62 (13.7)	87 (23.5)	<.001*
Stage			
I + II		261 (70.4)	
III + IV		110 (29.6)	
Tumor T status			
≤T2		318 (85.7)	
>T2		53 (14.3)	
Lymph node status			
N0		258 (69.5)	
N1 + N2 + N3		113 (30.5)	
Metastasis			
M0		301 (81.1)	
M1		70 (18.9)	
Sub-group types			
NSCLC		351 (94.6)	
SCLC		20 (5.4)	
Histology			
Adenocarcinoma		279 (75.2)	
Squamous-cell carcinoma		56 (15.1)	
Other carcinoma		36 (9.7)	

Mann–Whitney *U* test or Fisher exact test was used between controls and patients with lung cancer.
NSCLC = nonsmall-cell lung cancer, SCLC = small-cell lung cancer.
* $P < .05$ as statistically significant.

3. Results

In this study, we evaluated differences in the general demographic characteristics of 371 patients with lung cancer and 451 cancer-free controls. All patients and participants were Chinese Han individuals (Table 1). There were no differences in age, cigarette smoking, alcohol consumption (all $P < .001$), and sex ($P = .537$). According to the American Joint Committee on Cancer (AJCC) TNM staging system, our results showed that 261 patients with lung cancer had clinical stage I + II (70.4%), and 110 patients had clinical stage III + IV (29.6%). The patients of lung cancers were divided into various subgroups, including nonsmall-cell lung cancer (NSCLC), small-cell lung cancer (SCLC), adenocarcinoma, squamous-cell carcinoma, and other carcinoma.

To evaluate whether the 4 *RETN* SNPs (rs7408174, rs1862513, rs3219175, and rs3745367) were associated with the risk of lung cancer, we genotyped controls and patients. Genotyping distributions and associations between lung cancer and *RETN* gene polymorphisms are illustrated in Table 2. The alleles with the highest distribution frequency at *RETN* rs3745367, rs7408174, rs1862513, and rs3219175 in both patients with lung cancer and control individuals were heterozygous A/G, homozygous T/T, heterozygous C/G, and homozygous G/G, respectively. Individuals carrying AG and AG + AA at rs3219175 had a 1.372-fold (95% CI: 0.533–0.961, $P < .05$) and 1.333-fold (95% CI: 1.010–1.761, $P < .05$) higher

Table 2

Distribution frequency of *RETN* genotypes in 451 controls and 371 patients with lung cancer.

Variable	Controls N = 451 (%)	Patients N = 371 (%)	OR (95% CI)	*P*
rs3745367				
GG	190 (42.1)	164 (44.2)	1.00 (reference)	
AG	194 (43.0)	164 (44.2)	0.979 (0.729–1.315)	.890
AA	67 (14.9)	43 (11.6)	0.744 (0.481–1.150)	.182
AG + AA	261 (57.9)	207 (55.8)	0.919 (0.696–1.213)	.550
G allele	574 (53.8)	492 (46.2)	1.00 (reference)	
A allele	328 (56.9)	250 (43.3)	0.889 (0.725–1.090)	.259
rs7408174				
TT	253 (56.1)	206 (55.5)	1.00 (reference)	
TC	168 (37.3)	144 (38.8)	1.053 (0.789–1.405)	.727
CC	30 (6.7)	21 (5.7)	0.860 (0.478–1.547)	.614
TC + CC	198 (43.9)	165 (44.5)	1.023 (0.776–1.350)	.869
T allele	674 (54.8)	556 (45.2)	1.00 (reference)	
C allele	228 (55.1)	186 (44.9)	0.989 (0.791–1.237)	.992
rs1862513				
CC	182 (40.4)	164 (44.2)	1.00 (reference)	
CG	203 (45.0)	157 (42.3)	0.858 (0.638–1.155)	.312
GG	66 (14.6)	50 (13.5)	0.841 (0.550–1.284)	.422
CG + GG	269 (59.6)	207 (55.8)	0.854 (0.647–1.128)	.266
C allele	567 (53.9)	485 (46.1)	1.00 (reference)	
G allele	335 (56.6)	257 (43.4)	0.897 (0.732–1.098)	.293
rs3219175				
GG	213 (47.2)	149 (40.2)	1.00 (reference)	
AG	175 (38.8)	168 (45.3)	1.372 (1.019–1.848)*	.037*
AA	63 (14.0)	54 (14.6)	1.225 (0.806–1.864)	.342
AG + AA	238 (52.8)	222 (59.8)	1.333 (1.010–1.761)*	.042*
G allele	601 (56.3)	466 (43.7)	1.00 (reference)	
A allele	301 (52.2)	276 (47.8)	1.183 (0.965–1.449)	.106

The ORs and with their 95% CIs were estimated by logistic regression models.
CI = confidence interval, OR = odds ratio, RETN, resistin.
* $P < .05$ as statistically significant.

risk of lung cancer, respectively, than individuals carrying the wild-type GG polymorphic allele. Individuals with polymorphisms at rs3745367, rs7408174, and rs1862513 showed no significant associations with lung cancer risk relative to the risk in individuals with the wild-type genotype.

Next, *RETN* genotypes in patients with lung cancer were evaluated to clarify the role of *RETN* polymorphisms in clinical TNM stage, primary tumor size, lymph node metastasis, and distant metastasis. For 371 patients with lung cancer, a significant correlation between rs3219175 variants (GG vs AG; GG vs AG +AA) and tumor distant metastasis (OR: 1.885, 95% CI: 1.041–3.414, $P < .05$; OR: 1.875, 95% CI: 1.064–3.304, $P < .05$, respectively) was observed (Table 3). However, no significant differences were observed between *RETN* rs3219175 genotypes and clinicopathlogical status (data were not shown). The distribution frequency of clinical status in the NSCLC and SCLC is summarized in Table 4. A significant correlation between subgroup lung cancers (NSCLC vs SCLC) and clinical stage (OR:

Table 3

Odds ratio (OR) and 95% confidence interval (CI) of clinical status and *RETN* rs3219175 genotypic frequencies in 371 lung cancer patients.

Variable	GG N = 149 (%)	AG N = 168 (%)	OR (95% CI)	AG + AA N = 222 (%)	OR (95% CI)
Clinical stage					
Stage I/II	112 (75.2)	112 (66.7)	1.00	149 (67.1)	1.00
Stage III/IV	37 (24.8)	56 (33.3)	1.514 (0.926–2.473)	73 (32.9)	1.483 (0.931–2.362)
Tumor size					
≦T2	131 (87.9)	144 (85.7)	1.00	187 (84.2)	1.00
>T2	18 (12.1)	24 (14.3)	1.213 (0.630–2.336)	35 (15.8)	1.362 (0.740–2.509)
Lymph node metastasis					
No	106 (71.1)	114 (67.9)	1.00	152 (68.5)	1.00
Yes	43 (28.9)	54 (32.1)	1.168 (0.723–1.887)	70 (31.5)	1.135 (0.721–1.787)
Distant metastasis					
No	129 (86.6)	130 (77.4)	1.00	172 (77.5)	1.00
Yes	20 (13.4)	38 (22.6)	1.885 (1.041–3.414)*	50 (22.5)	1.875 (1.064–3.304)*

The ORs with analyzed by their 95% CIs were estimated by logistic regression models.
CI = confidence interval, OR = odds ratio, RETN, resistin.
* $P < .05$ as statistically significant.

Table 4

Distribution frequency of clinical status in 351 nonsmall-cell lung cancer (NSCLC) and 20 small-cell lung cancer (SCLC).

Variable	NSCLC N = 351 (%)	SCLC N = 20 (%)	OR (95% CI)	*P*
Clinical stage				
Stage I/II	260 (74.1)	1 (5.0)	1.00	
Stage III/IV	91 (25.9)	19 (95.0)	54.286 (7.165–411.275)*	<.001
Tumor size				
≦T2	306 (87.2)	12 (60.0)	1.00	
>T2	45 (12.8)	8 (40.0)	4.533 (1.757–11.695)*	.001
Lymph node metastasis				
No	257 (73.2)	1 (5.0)	1.00	
Yes	94 (26.8)	19 (95.0)	51.947 (6.859–393.441)*	<.001
Distant metastasis				
No	294 (83.8)	7 (35.0)	1.00	
Yes	57 (16.2)	13 (65.0)	9.579 (3.662–25.058)*	<.001

The odds ratio (OR) analyzed by their 95% confidence interval (CI) were estimated by logistic regression models.
CI = confidence interval, NSCLC = nonsmall-cell lung cancer, OR = odds ratio, SCLC = small-cell lung cancer.
* $P < .05$ as statistically significant.

54.286, 95% CI: 7.165–411.275, $P < .001$), tumor size (OR: 4.533, 95% CI: 1.757–11.695, $P = .001$), lymph node metastasis (OR: 51.947, 95% CI: 6.859–393.441, $P < .001$), and distant metastasis (OR: 9.579, 95% CI: 3.662–25.058, $P < .001$), respectively, were observed (Table 4). For 351 patients of NSCLC, a significant correlation between rs3219175 variants (GG vs AG; GG vs AG+AA) and tumor distant metastasis (OR: 1.984, 95% CI: 1.037–3.796, $P < .05$; OR: 1.922, 95% CI: 1.032–3.581, $P < .05$, respectively) was observed (Table 5). However, there was no significant difference between the lung adenocarcinoma and squamous cell carcinoma with polymorphisms of the resistin genotypes (data were not shown).

For the indicated correlations, we continued to employ Genotype-Tissue Expression (GTEx) datasets to further evaluate the association between rs3219175 and *RETN* expression. A significant alteration in RETN expression was observed in lung tissues and whole blood of patients with the polymorphic allele of *RETN* rs3219175 in the GTEx database. We observed that the heterozygous genotypes at rs3219175 were positively associated with RETN expression, compared with the wild-type homozygous genotypes ($P < .05$; Fig. 1A, B) (GTEx dataset # ENSG00000104918.4). These data suggested that the expression and function of RETN in response to genetic polymorphisms may affect lung cancer progression.

4. Discussion

Lung cancer is one of the most malignant cancers reported to date and is associated with severe morbidities and high mortality rates worldwide. Neither traditional chemotherapy nor molecular targeted therapy is efficacious in the clinical treatment of lung cancer.[14] It is imperative that increasing genetic studies and signaling mechanisms might help to clarify a proper strategy for lung cancer treatment. In this present study, we found that *RETN* gene polymorphisms were associated with a higher susceptibility to lung cancer. Indeed, our results showed that the ratios of cigarette smokers/nonsmokers in controls (90.5:9.5) and patients with lung cancer (60.4:39.6) were relatively normal, similar to the ratios of alcohol consumption/no alcohol consumption in controls and patients. Our findings showed that in the Chinese Han population, smoking and alcohol consumption were related to the risk of developing lung cancer.

RETN is an adipokine that is associated with obesity, inflammation, and various cancers. A recent study has reported

Table 5

Association of *RETN* rs3219175 genotypic frequencies with laboratory status in NSCLC patients.

Variable	GG N = 142 (%)	AG N = 159 (%)	OR (95% CI)	AG + AA N = 209 (%)	OR (95% CI)
Clinical stage					
Stage I/II	111 (78.2)	112 (70.4)	1.00	149 (71.3)	1.00
Stage III/IV	31 (21.8)	47 (29.6)	1.503 (0.890–2.537)	60 (28.7)	1.442 (0.876–2.373)
Tumor size					
≦ T2	128 (90.1)	136 (85.5)	1.00	178 (85.2)	1.00
> T2	14 (9.9)	23 (14.5)	1.546 (0.763–3.135)	31 (14.8)	1.592 (0.814–3.114)
Lymph node metastasis					
No	105 (73.9)	114 (71.7)	1.00	152 (72.7)	1.00
Yes	37 (26.1)	45 (28.3)	1.120 (0.673–1.864)	57 (27.3)	1.064 (0.657–1.725)
Distant metastasis					
No	126 (88.7)	127 (79.9)	1.00	168 (80.4)	1.00
Yes	16 (11.3)	32 (20.1)	1.984 (1.037–3.796)*	41 (19.6)	1.922 (1.032–3.581)*

The OR with analyzed by their 95% confidence interval CI were estimated by logistic regression models.
CI = confidence interval, NSCLC = nonsmall-cell lung cancer, OR = odds ratio, RETN, resistin.
* $P < .05$ as statistically significant.

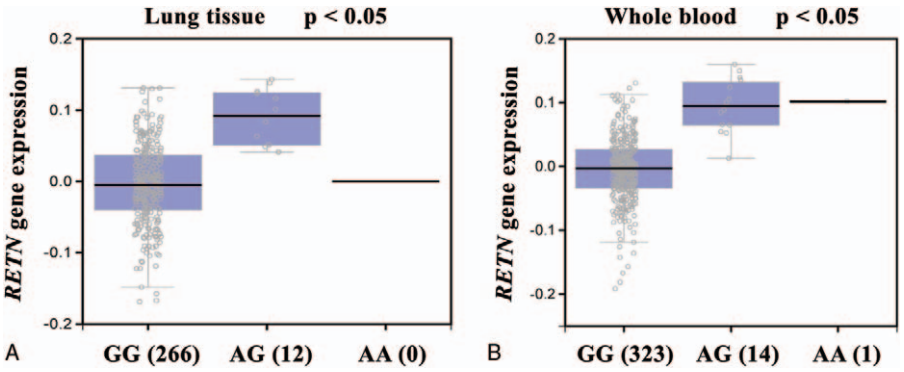

Figure 1. Functional analysis of the RETN SNP rs3219175 in lung cancer progression according to the Genotype-Tissue Expression (GTEx) dataset. (A) Correlation of rs3219175 genotypes with RETN mRNA expression in lung cancer tissue and (B) whole blood.

that resistin level was found to be higher in the lung cancer (NSCLC) patients and associated with cancer cachexia.[15] Accumulating evidence has shown that the *RETN* gene often shows genetic or epigenetic alterations. Moreover, genetic polymorphisms in *RETN* have been identified in colorectal, colon, and breast cancers.[13,16,17] A recent SNP study demonstrated that *RETN* SNPs in the promoter region of the gene were negatively associated with DNA methylation in patients with type 2 diabetes.[18] In the present study, we showed, for the first time, that 1 of 4 *RETN* gene polymorphisms was associated with a high incidence of lung cancer. Indeed, our results indicated that AG or AG + AA at rs3219175 was significantly correlated with an increased lung cancer risk after 4 RETN polymorphisms genotyping in case–control subjects. In contrast, *RETN* polymorphisms at rs7408174, rs1862513, and rs3745367 were not significantly related to the risk of lung cancer compared with that in controls. Importantly, a previous study showed that this *RETN* SNP (rs3219175) positively affected the response to interferon-based anti-hepatitis C virus therapy.[19] Thus, our results may provide insights into the development of targeted therapy for lung cancer in patients with this specific SNP.

In epigenetic DNA methylation, variant polymorphisms in the promoter region could regulate gene expression and impact the risk of lung cancer.[20] The rs3219175 polymorphism is located in the promoter region and may regulate *RETN* gene expression. However, the reconstructed linkage disequilibrium plot of the 4 *RETN* SNPs showed that rs3219175 had low linkage disequilibrium with rs1862513 (data was not shown). In addition, our results demonstrated that patients with lung cancer carrying at least 1 A allele at rs3219175 were at a higher risk of tumor metastasis. A previous study revealed that the presence of the polymorphic allele of RETN rs3219175 was associated with dramatic effects on plasma resistin in patients with type 2 diabetes.[10] Another previous report had showed that rs3219175 SNPs were significant associated with log-resistin levels in Malaysian Malays.[21] In this study, we did not perform a detailed functional analysis between rs3219175 SNPs and resistin levels in Chinese Han populations, though it required to be further studied in the future. The issue of how these SNPs affect resistin gene expression in lung cancer cells is required to be further clarified. Thus, further studies are also needed to assess the correlations between *RETN* polymorphisms and lung cancer progression.

Although our present results showed that smoking and alcohol consumption were the risk factors for lung cancer (Table 1, $P < .001$), we failed to find a significant association after controlling for smoking and alcohol consumption in the Chinese Han population (data were not shown) because of poor records of smoking and alcohol consumption in these patients. In addition, some patient survival data were unavailable because patients had just recently enrolled in the study. Further studies are needed using larger populations of patients to confirm the role of *RETN* polymorphisms in lung cancer progression. Furthermore, the functional role of RETN in metastasis in patients with lung cancer should also be evaluated.

Taken together, our results demonstrated the association between 1 *RETN* gene variant and risk of lung cancer and found that *RETN* rs3219175 was significantly associated with tumor distant metastasis in the Chinese Han population. This study is the first to report a correlation between *RETN* polymorphisms and lung cancer risk. Thus, *RETN* could be developed as a genetic prognostic marker for lung cancer therapy.

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