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No Association between *PIK3CA* Polymorphism and Lung Cancer Risk in the Korean Population

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Abstract

The *PIK3CA* gene, oncogenic gene located on human chromosome 3q26.3, is an important regulator of cell proliferation, death, motility and invasion. To evaluate the role of *PIK3CA* gene in the risk of Korean lung cancer, genotypes of the *PIK3CA* polymorphisms (rs11709323, rs2699895, rs3729679, rs17849074 and rs1356413) were determined in 423 lung cancer patients and 443 normal controls. Statistical analyses revealed that the genotypes and haplotypes in the *PIK3CA* gene were not significantly associated with the risk of lung cancer in the Korean population, suggesting that these *PIK3CA* polymorphisms do not contribute to the genetic susceptibility to lung cancer in the Korean population.

Keywords: lung cancer, *PIK3CA*, polymorphism

Introduction

Lung cancer has been the leading cause of cancer-related deaths in Korea, and its incidence continues to rise (Shin *et al*., 2007). Nevertheless, prognosis of lung cancer remains largely poor despite innovations in diagnostic testing, surgical technique, and development of new chemotherapeutic agents. Recently introduced targeted agents show different response according to histologic subtype, and the efficiency of treatment modalities for lung cancer depends on the time of diagnosis (Brambilla *et al*., 2001). Therefore, there is a great need for rapid and efficient early detection methods. Therefore, in order to develop improved molecular biomarkers for early detection and prediction of response to chemotherapy, it is important to identify genetic alterations specific to each subtype of lung cancer. Single nucleotide polymorphisms (SNPs) have an excellent potential to be used as biomarkers for diagnosing genetic diseases, including cancers, compared to other less common polymorphisms and microsatellite markers.

Phosphatidylinositol 3-kinases (PI3Ks) are a family of lipid protein kinases that regulate various cellular functions, including cell proliferation, survival, motility, and adhesion (Engelman *et al*., 2006). The *PIK3CA* gene encodes a catalytic subunit p110α of class IA PI3Ks that is located in the downstream signaling pathway of growth factor receptors, such as EGFR and HER2 oncoproteins; the pathway is negatively regulated by the PTEN tumor suppressor protein. One of the most important downstream targets of the p110α complex in cancer is AKT, which up-regulates cell survival, proliferation, and growth signaling through phosphorylating multiple substrates, including apoptosis-related proteins (BAD and FKHR) and the mTOR complex components (PRAS40 and mTOR) (Manning and Cantley, 2007).

Somatic mutations of the *PIK3CA* gene have been reported in a wide range of human cancers, being especially frequent in breast, colorectal, ovary and liver tumors (Karakas *et al*., 2006). Mutation of the *PIK3CA* is likely to function as an oncogene in human cancers (Kang *et al*., 2005), however, the mutation rate shown in lung cancer is relatively low (Kawano *et al*., 2006; Lee *et al*., 2005; Samuels *et al*., 2004). Furthermore, mutation and copy number gain of the *PIK3CA* gene have been reported to be associated with lung cancer (Massion *et al*., 2002; Yamamoto *et al*., 2008), nevertheless, the association between polymorphism and the risk of lung cancer has not yet been fully clarified.

This study was undertaken to examine the polymorphism of *PIK3CA*, and its relation with the risk of lung cancer in Korean population. To our best knowledge, this is the first report on the polymorphism of *PIK3CA* in lung cancer patients in Korean population.

Methods

Study subjects

Between August 2001 and November 2007, blood sam-

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ples were collected from 866 subjects, including 423 lung cancer patients and 443 normal controls without cancer. Lung cancer patients were recruited from the patient pool at the Genomic Research Center for Lung and Breast/Ovarian Cancer, and control subjects were randomly selected from a pool of healthy volunteers who had visited the Cardiovascular Genome Center and Genomic Research Center for Allergy and Respiratory Diseases. Detailed information on diet, smoking status, drinking status, lifestyle, and medical history were collected by a trained interviewer using a structured questionnaire. Out of 423 cases, 413 smoking status, 335 stage, and 407 cell types were available for characteristic information, while 341 smoking status out of 443 controls were available for characteristic information (Table 1). All study subjects provided written consents and were ethnic Koreans, and all the participating Institutional Review Boards approved the study protocol.

Preparation of genomic DNA and genotyping

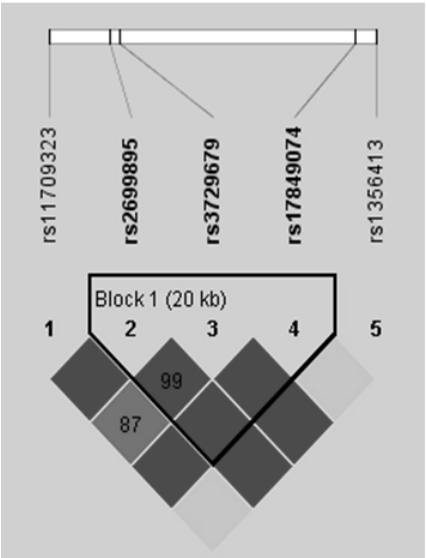
Genomic DNA was prepared from peripheral blood samples using a Puregene blood DNA kit (Gentra, Minneapolis, MN, USA), according to the manufacture's protocol. We performed genotyping for the five polymorphisms (rs11709323, rs2699895, rs3729679, rs17849074 and rs1356413). Genotyping was done by the SNP-IT assay using the SNPstream 25K System (Orchid Biosciences, Princeton, NJ, USA). Briefly, the genomic DNA region spanning the polymorphic site was amplified polymerase chain reaction (PCR) by one phosphothiolated primer and one regular PCR primer. The amplified PCR products were then digested with T7 exonuclease. The 5' phosphothiolates protected one strand of the PCR product from T7 exonuclease digestion, resulting in the generation of a single-stranded PCR template. The single-stranded PCR template was overlaid on a 384-well plate that contained a covalently attached SNP-IT pri-

Table 1. Baseline characteristics of the study subjects

Variable	Case (%)	Control (%)
Age (years)	61.5±10.2	60.0±11.2
Gender		
Male	313 (74.0)	312 (70.4)
Female	110 (26.0)	131 (29.6)
Smoking status		
Smoker	300 (72.6)	151 (44.3)
Non-smoker	113 (27.4)	190 (55.7)
Stage		
1-3a	90 (26.9)	
3b-4	245 (73.1)	
Cell type		
Adenocarcinomas	169 (41.5)	
Sguamus carcinomas	129 (31.7)	
Other carcinomas	109 (26.8)	

Other carcinomas include the small cell, large cell, and mixed cell carcinomas or undifferentiated carcinomas.

A. LDs among *PIK3CA* polymorphisms



r2 \ D'	rs11709323	rs2699895	rs3729679	rs17849074	rs1356413
rs11709323		1	0.872	1	1
rs2699895	0.026		0.996	1	1
rs3729679	0.020	0.980		1	1
rs17849074	0.016	0.030	0.030		1
rs1356413	0.005	0.177	0.175	0.005	

B. Haplotypes in *PIK3CA*

Haplotype	Frequency
C-A-T	0.696
A-G-T	0.182
C-A-C	0.119
C-G-T	0.002
A-A-T	0.001

Fig. 1. Location of polymorphisms in the *PIK3CA* gene, linkage disequilibrium (LD) and haplotypes. (A) LD coefficients (|D'| and r^2) were calculated among single nucleotide polymorphisms, based on the genotypes of whole study subjects (n=866). (B) Haplotypes of *PIK3CA* in the Korean population. Haplotypes with frequency over 0.001 are presented.

mer extension primer designed to hybridize immediately adjacent to the polymorphic site. The SNP-IT primer was extended for a single base with DNA polymerase and a mixture of appropriate acycloterminators complementary to the polymorphic nucleotide that were labeled with either fluorescein isothiocyanate (FITC) or biotin. The identity of the incorporated nucleotide was determined by serial colorimetric reactions with anti-FITC-AP and streptavidin-horseradish peroxidase, respectively. Resultant yellow and/or blue color development was analyzed using an ELISA reader, and the final genotype calls were made using a QCReview program (Orchid Biosciences).

Statistical analysis

Allele frequencies, genotype frequencies, and departures of genotype distributions from Hardy-Weinberg equilibrium for each SNP were analyzed using the chi-square test or Fisher's exact test. A p-value of <0.05 was considered statistically significant. Linkage disequilibrium (LD) was tested on pairwise combinations of polymorphisms using the absolute value of the standardized measure of LD, D' calculated by the Haploview program version 3.2. The haplotypes and their frequencies were estimated by the Haploview program version 3.2. Genotype-specific risks were estimated as odds ratios (ORs) with associated 95% confidence intervals by unconditional logistic regression (SAS version 9.1; SAS Institute, Cary, NC, USA) and adjusted for age, gender and smoking status.

Results

Among 219 polymorphisms of *PIK3CA* gene recorded in the dbSNP (www.nci.nlm.nih.gov/SNP), five polymorphisms (rs11709323, rs2699895, rs3729679, rs17849074 and rs1356413) were selected and analyzed on the basis of reported frequency in Asian population. The genotype distributions of the polymorphisms among the pop-

Table 2. Distribution of genotype and their association with lung cancer risk in Korean lung cancer patients

Subgroup	rs#	Genotype	Case (%)	Control (%)	Dominant	Recessive	Codominant
					aOR[a]	aOR	aOR
Overall	rs11709323	TT	343 (81.67)	341 (78.57)			
		TC	72 (17.14)	85 (19.59)	0.83 (0.50-1.39)	1.71 (0.23-12.76)	0.88 (0.55-1.41)
		CC	5 (1.19)	8 (1.84)			
	rs2699895	CC	292 (69.03)	283 (65.36)			
		CA	116 (27.42)	139 (32.1)	0.82 (0.54-1.26)	1.58 (0.47-5.28)	0.90 (0.62-1.31)
		AA	15 (3.55)	11 (2.54)			
	rs3729679	AA	290 (68.72)	284 (65.74)			
		AG	117 (27.73)	133 (30.79)	0.85 (0.56-1.30)	1.60 (0.49-5.18)	0.93 (0.64-1.34)
		GG	15 (3.55)	15 (3.47)			
	rs17849074	TT	395 (93.38)	404 (91.82)			
		TC	27 (6.38)	36 (8.18)	0.95 (0.44-2.08)		1.00 (0.47-2.13)
		CC	1 (0.24)	0 (0)			
	rs1356413	CC	323 (76.54)	344 (78.9)			
		CG	91 (21.56)	87 (19.95)	1.08 (0.67-1.75)	4.89 (0.53-45.11)	1.16 (0.74-1.81)
		GG	8 (1.9)	5 (1.15)			
Male	rs11709323	TT	252 (81.29)	235 (77.3)			
		TC	55 (17.74)	64 (21.05)	0.82 (0.44-1.52)	2.30 (0.07-71.74)	0.86 (0.48-1.54)
		CC	3 (0.97)	5 (1.64)			
	rs2699895	CC	217 (69.33)	199 (65.89)			
		CA	85 (27.16)	95 (31.46)	0.84 (0.49-1.43)	1.42 (0.30-6.64)	0.91 (0.57-1.44)
		AA	11 (3.51)	8 (2.65)			
	rs3729679	AA	216 (69.23)	199 (66.11)			
		AG	86 (27.56)	90 (29.9)	0.88 (0.51-1.49)	1.18 (0.26-5.30)	0.92 (0.58-1.46)
		GG	10 (3.21)	12 (3.99)			
	rs17849074	TT	291 (92.97)	283 (91.59)			
		TC	22 (7.03)	26 (8.41)	1.16 (0.45-3.04)		1.16 (0.45-3.04)
		CC	0 (0)	0 (0)			
	rs1356413	CC	231 (74.04)	245 (80.33)			
		CG	76 (24.36)	56 (18.36)	1.54 (0.83-2.84)	8.45 (0.37-194.65)	1.60 (0.90-2.85)
		GG	5 (1.6)	4 (1.31)			

Table 2. Continued

Subgroup	rs#	Genotype	Case (%)	Control (%)	Dominant	Recessive	Codominant
					aOR[a]	aOR	aOR
Female	rs11709323	TT	91 (82.73)	106 (81.54)			
		TC	17 (15.45)	21 (16.15)	0.93 (0.37-2.33)	1.29 (0.10-17.37)	0.97 (0.44-2.15)
		CC	2 (1.82)	3 (2.31)			
	rs2699895	CC	75 (68.18)	84 (64.12)			
		CA	31 (28.18)	44 (33.59)	0.79 (0.38-1.63)	1.70 (0.23-12.68)	0.88 (0.46-1.67)
		AA	4 (3.64)	3 (2.29)			
	rs3729679	AA	74 (67.27)	85 (64.89)			
		AG	31 (28.18)	43 (32.82)	0.83 (0.40-1.74)	2.13 (0.31-14.65)	0.95 (0.51-1.78)
		GG	5 (4.55)	3 (2.29)			
	rs17849074	TT	104 (94.55)	121 (92.37)			
		TC	5 (4.55)	10 (7.63)	0.72 (0.17-3.03)		0.89 (0.24-3.23)
		CC	1 (0.91)	0 (0)			
	rs1356413	CC	92 (83.64)	99 (75.57)			
		CG	15 (13.64)	31 (23.66)	0.56 (0.23-1.34)	2.63 (0.11-63.42)	0.65 (0.29-1.45)
		GG	3 (2.73)	1 (0.76)			
Smoker	rs11709323	TT	242 (81.48)	116 (78.38)			
		TC	53 (17.85)	31 (20.95)	0.88 (0.45-1.71)	0.62 (0.03-14.98)	0.87 (0.46-1.65)
		CC	2 (0.67)	1 (0.68)			
	rs2699895	CC	204 (68)	98 (65.33)			
		CA	86 (28.67)	47 (31.33)	0.94 (0.53-1.67)	1.06 (0.23-4.89)	0.96 (0.59-1.58)
		AA	10 (3.33)	5 (3.33)			
	rs3729679	AA	202 (67.56)	98 (65.77)			
		AG	88 (29.43)	46 (30.87)	1.00 (0.56-1.78)	0.97 (0.20-4.61)	1.00 (0.61-1.65)
		GG	9 (3.01)	5 (3.36)			
	rs17849074	TT	277 (92.33)	142 (94.04)			
		TC	23 (7.67)	9 (5.96)	1.54 (0.52-4.59)		1.54 (0.52-4.59)
		CC	0	0			
	rs1356413	CC	222 (74.25)	121 (80.67)			
		CG	74 (24.75)	28 (18.67)	1.47 (0.76-2.84)	1.54 (0.08-31.05)	1.43 (0.77-2.68)
		GG	3 (1)	1 (0.67)			
Non-smoker	rs11709323	TT	94 (83.19)	149 (79.26)			
		TC	16 (14.16)	37 (19.68)	0.85 (0.38-1.93)	2.40 (0.21-26.90)	0.96 (0.47-1.95)
		CC	3 (2.65)	2 (1.06)			
	rs2699895	CC	79 (69.91)	114 (60.64)			
		CA	29 (25.66)	70 (37.23)	0.68 (0.35-1.34)	1.96 (0.32-11.96)	0.80 (0.45-1.44)
		AA	5 (4.42)	4 (2.13)			
	rs3729679	AA	79 (69.91)	116 (61.05)			
		AG	28 (24.78)	69 (36.32)	0.70 (0.36-1.37)	2.00 (0.38-10.44)	0.84 (0.47-1.48)
		GG	6 (5.31)	5 (2.63)			
	rs17849074	TT	108 (95.58)	172 (91.01)			
		TC	4 (3.54)	17 (8.99)	0.51 (0.12-2.00)		0.64 (0.19-2.20)
		CC	1 (0.88)	0 (0)			
	rs1356413	CC	93 (82.3)	147 (77.37)			
		CG	16 (14.16)	42 (22.11)	0.73 (0.33-1.61)	8.45 (0.44-163.91)	0.92 (0.46-1.84)
		GG	4 (3.54)	1 (0.53)			

[a]aOR and confidence interval (95% CI) were calculated by unconditional logistic regression, adjusted for age, gender and smoking history.

ulation were in Hardy-Weinberg equilibrium. Also, LD coefficients (|D'| and r^2) and haplotypes among the polymorphisms were calculated (Fig. 1). Haplotype block included rs2699895, rs3729679 and rs17849074 among the five polymorphisms.

Association of lung cancer risk with *PIK3CA* polymorphisms was then analyzed (Table 2), revealing no association of the five polymorphisms with the risks of

lung cancer. The association of the polymorphisms with the risk of lung cancer was further examined after stratifying the subjects according to gender and smoking status. However, subsequent analysis also revealed no significant association. Furthermore, the haplotypes (C-A-T, A-G-T and C-A-C) of *PIK3CA* polymorphisms were not associated with the risks of lung cancer in three alternative models (Table 3).

Table 3. Association analysis of haplotype with lung cancer risk in Korean lung cancer patients

Subgroup	Haplotype	Haplotype pair	Case (%)	Control (%)	Dominant	Recessive	Codominant
					aOR[a]	aOR	aOR
Overall	C-A-T	+/+	202 (47.98)	207 (49.29)			
		+/−	184 (43.71)	177 (42.14)	0.93 (0.47-1.84)	1.00 (0.69-1.46)	0.99 (0.74-1.33)
		−/−	35 (8.31)	36 (8.57)			
	A-G-T	+/+	14 (3.33)	11 (2.62)			
		+/−	116 (27.55)	130 (30.95)	0.83 (0.56-1.24)	1.50 (0.48-4.70)	0.91 (0.64-1.28)
		−/−	291 (69.12)	279 (66.43)			
	C-A-C	+/+	8 (1.9)	5 (1.19)			
		+/−	91 (21.62)	85 (20.24)	1.07 (0.68-1.67)	4.83 (0.61-38.02)	1.14 (0.75-1.73)
		−/−	322 (76.48)	330 (78.57)			
Male	C-A-T	+/+	145 (46.62)	148 (51.21)			
		+/−	140 (45.02)	116 (40.14)	0.84 (0.35-1.98)	0.80 (0.50-1.28)	0.84 (0.58-1.23)
		−/−	26 (8.36)	25 (8.65)			
	A-G-T	+/+	10 (3.22)	8 (2.77)			
		+/−	85 (27.33)	87 (30.1)	0.85 (0.52-1.40)	1.31 (0.30-5.67)	0.90 (0.58-1.40)
		−/−	216 (69.45)	194 (67.13)			
	C-A-C	+/+	5 (1.61)	4 (1.38)			
		+/−	76 (24.44)	54 (18.69)	1.51 (0.85-2.66)	8.24 (0.45-151.61)	1.57 (0.92-2.68)
		−/−	230 (73.95)	231 (79.93)			
Female	C-A-T	+/+	57 (51.82)	59 (45.04)			
		+/−	44 (40)	61 (46.56)	1.17 (0.36-3.78)	1.47 (0.77-2.81)	1.31 (0.78-2.18)
		−/−	9 (8.18)	11 (8.4)			
	A-G-T	+/+	4 (3.64)	3 (2.29)			
		+/−	31 (28.18)	43 (32.82)	0.81 (0.41-1.61)	1.70 (0.26-11.01)	0.90 (0.50-1.64)
		−/−	75 (68.18)	85 (64.89)			
	C-A-C	+/+	3 (2.73)	1 (0.76)			
		+/−	15 (13.64)	31 (23.66)	0.56 (0.25-1.26)	2.63 (0.14-50.65)	0.65 (0.31-1.37)
		−/−	92 (83.64)	99 (75.57)			
Smoker	C-A-T	+/+	136 (45.64)	75 (50.68)			
		+/−	138 (46.31)	60 (40.54)	0.97 (0.39-2.44)	0.77 (0.47-1.28)	0.85 (0.57-1.26)
		−/−	24 (8.05)	13 (8.78)			
	A-G-T	+/+	9 (3.02)	5 (3.38)			
		+/−	86 (28.86)	46 (31.08)	0.96 (0.56-1.64)	0.96 (0.23-4.13)	0.97 (0.61-1.54)
		−/−	203 (68.12)	97 (65.54)			
	C-A-C	+/+	3 (1.01)	1 (0.68)			
		+/−	74 (24.83)	28 (18.92)	1.44 (0.78-2.67)	1.51 (0.09-24.76)	1.41 (0.79-2.53)
		−/−	221 (74.16)	119 (80.41)			
Non-smoker	C-A-T	+/+	59 (52.21)	82 (43.62)			
		+/−	44 (38.94)	90 (47.87)	0.97 (0.34-2.73)	1.37 (0.77-2.46)	1.21 (0.76-1.91)
		−/−	10 (8.85)	16 (8.51)			
	A-G-T	+/+	5 (4.42)	4 (2.13)			
		+/−	29 (25.66)	69 (36.7)	0.71 (0.38-1.31)	1.96 (0.36-10.52)	0.82 (0.48-1.41)
		−/−	79 (69.91)	115 (61.17)			
	C-A-C	+/+	4 (3.54)	1 (0.53)			
		+/−	16 (14.16)	42 (22.34)	0.72 (0.35-1.51)	8.33 (0.53-130.77)	0.91 (0.48-1.73)
		−/−	93 (82.3)	145 (77.13)			

[a]aOR and confidence interval (95% CI) were calculated by unconditional logistic regression, adjusted for age, gender and smoking history.

Discussion

Most human malignancies are caused by somatic variations within the cancer genome, leading to activation of oncogenes or inactivation of tumor suppressor genes, and many of the resultant changes target cell signaling pathways (Vogelstein and Kinzler, 2004). PI3K/AKT pathway is the major pathway controlling cell growth and tumorigenesis (Cantley, 2002; Katso *et al*., 2001; Vivanco and Sawyers, 2002), and the pathway lies downstream of receptor tyrosine kinase, including EGFR. In addition to *PIK3CA*, other components of the pathway, including the loss of the inhibitor PTEN or activating mutation of AKT, occurs in certain cancers (Samuels and Ericson, 2006; Shibata *et al*., 2009).

Recently, a few studies revealed genetic variations of *PIK3CA* gene in colon, rectal and bladder cancer risk (Chen *et al*., 2009; Slattery *et al*., 2010), however, there has been no study done on the association between lung cancer risk and polymorphism of *PIK3CA* gene in the Korean population. In this study, we hypothesized that *PIK3CA* polymorphisms are associated with lung cancer risk. However, our finding indicated no association between *PIK3CA* polymorphisms and lung cancer risk in the Korean population.

Genetic variations often show ethnic variation (Kim *et al*., 2006; Kim *et al*., 2008). In the present study, the observed frequencies of the minor alleles of rs11709323, rs2699895, rs3729679, rs17849074 and rs1356413 were 0.116, 0.186, 0.189, 0.041 and 0.111, respectively. According to the HapMap database, the frequencies of the minor alleles in Asian ethnic groups (Han Chinese and Japanese) were shown to be 0.045, 0.148, 0.193, 0.045 and 0.039, respectively, thus showing similar frequencies to the present study.

A series of our previous studies showed that polymorphisms of oncogene, tumor suppressor gene and receptor tyrosine kinase are related to lung cancer risk (Choi *et al*., 2009; Jo *et al*., 2008; Kim *et al*., 2010; Sung *et al*., 2008). On the other hand, however, the genotypes of *PIK3CA* gene polymorphisms, determined in 866 Koreans in the present study, revealed no significant difference between lung cancer patients and normal controls. This result suggests that *PIK3CA* gene polymorphisms are not likely to play a major role in the susceptibility of Korean to lung cancer.

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