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ORIGINAL ARTICLE

Association study of *TP53* polymorphisms with lung cancer in a Korean population

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Abstract The tumor suppressor gene, *TP53*, is located on chromosome 17p13.1 and is critical for DNA repair, cell-cycle control, and apoptosis. *TP53* also plays a crucial function in the tumorigenesis of lung cancer. Inactivation of *TP53* via genetic alterations such as missense mutations is often associated with lung cancer. In this study, potential association of *TP53* polymorphisms with the risk of lung cancer was examined in a Korean population. A total of 299 Korean lung cancer patients and 296 control subjects were recruited into this study. Direct DNA sequencing and TaqMan analysis were employed, and logistic regression analyses were conducted to characterize the association between *TP53* polymorphisms and lung cancer risk. Through direct sequencing in 24 Korean individuals, 13 sequence variants were identified, and five of these polymorphisms were selected for a larger-scale genotyping ($n = 595$). Statistical analyses revealed that polymorphisms and haplotypes in the *TP53* gene, including Arg72Pro, were not significantly associated with lung cancer in a Korean population.

Keywords Tumor protein p53 *(TP53)* · Korean population · Haplotypes · Lung cancer · Single nucleotide polymorphisms

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Introduction

Lung cancer is one of the most common cancers and has the highest mortality rate among all cancers in Korea (Shin et al. 2005). It is a multicellular and multistage process (Hazelton et al. 2005) that involves a number of genetic changes in oncogenes and tumor suppressor genes (Sanchez-Cespedes 2003; Toloza et al. 2006). Tumor suppressor genes such as *FHIT* and *PTEN* are frequently inactivated in lung cancer by genetic alterations, including chromosomal deletions and mutations (Sozzi et al. 1998; Yokomizo et al. 1998). In particular, *TP53* (OMIM no. 191170) is considered to be the most commonly inactivated gene by genetic alteration in a large proportion of lung cancer (Hollstein et al. 1991). As a typical tumor suppressor gene, *TP53*, located on chromosome 17p13.1, is critical for DNA repair, cell-cycle control, and apoptosis (Fuster et al. 2007), and its gene alterations have frequently been found in most human cancers (Hainaut and Hollstein 2000; Zambetti 2007). In particular, *TP53* mutation is

present in more than 90% of small-cell lung cancers (SCLC) and more than 50% of non-small-cell lung cancers (NSCLC) (Wistuba et al. 2001). Inactivation of *TP53* in lung cancers leads to its loss of function as a transcription factor (Soussi 2007). Recently, much research has focused on the possible association between polymorphisms of *TP53* gene-related lung cancer susceptibility, and the most extensively studied single nucleotide polymorphism (SNP) is a G/C variation at the second position of codon 72 in exon 4, leading to Arg72 or Pro72 protein (Petitjean et al. 2007). A few studies showed that codon 72 polymorphisms in the *TP53* gene are significantly associated with an increased lung cancer risk (Nadji et al. 2007; Popanda et al. 2007). On the other hand, no association between this polymorphisms and lung cancer development has been reported (Khadang et al. 2007; Rajaraman et al. 2007). Although numerous studies have analyzed the impact of codon 72 polymorphisms in the *TP53* on cancer risk, these results remain largely contradictory, and no clear consensus has been reached. In this study, we attempted to characterize the association between these *TP53* polymorphisms and the risk of lung cancer development in a Korean population by using genotype and haplotype analysis. Our finding indicated that *TP53* polymorphisms and haplotypes, including Arg72Pro, are not significantly associated with lung cancer risk in a Korean population.

Materials and methods

Study subjects

This case-control study included 299 lung cancer patients and 296 healthy controls. The clinical characteristics of these subjects are summarized in Table 1. The eligible cases included all patients diagnosed with primary lung cancer at the Korea University Medical Center in Korea from October 2001 to April 2004. Lung cancer patients were recruited from the patient pool at the Genomic Research Center for Lung and Breast/Ovarian Cancers, and the control subjects were randomly selected from a pool of healthy volunteers who had previously visited the Cardiovascular Genome Center. Control subjects were selected from volunteers who had been screened with routine physical examination, past history, and laboratory tests, including cancer screening and diagnosis. Although specific cancer diagnostic examinations were not performed in these volunteers, chest radiograph, blood examination, and urinalysis were taken to exclude concomitant overt diseases. A detailed questionnaire, including diet, smoking status, drinking status, lifestyle, and medical history, was completed by each patient and control subject with the help of a trained interviewer. As for smoking status, anyone who reported smoking at least once a day was considered to be a smoker for the purpose of this study. Study subjects were approved by the Institutional Review Board of the Korea University Medical Center.

Table 1 Demographic characteristics among lung cancer cases and controls

	Control	Case	*P* value
Number of subjects	296	299	
Age (years, mean ± standard deviation)	51.8 ± 13.2	62.3 ± 10.3	<0.0001
Gender			
Male	283	219	<0.0001
Female	16	80	
Smoking status			
Never	90	76	0.009
Current	204	204	
Unknown	5	19	

Sequence analysis

We sequenced all exons and their boundaries, including the promoter region, of the *TP53* gene in 24 Korean DNA samples, using the ABI Prism 3700 DNA analyzer (Applied Biosystems, Foster City, CA, USA). All primer sets for amplification and sequence analysis were designed on the basis of GenBank sequences [Electronic supplementary material (ESM), Table 1]. The primer of the related information can be accessed at our Web site (http://www.snp-genetics.com/user/additional_list.asp).

Genotyping with fluorescence polarization detection

To genotype the polymorphic sites, all amplifying primers and probes were designed for the TaqMan system (ESM Table 2). Primer Express (Applied Biosystems) was used to design both the polymerase chain reaction (PCR) primers and the minor groove binder (MGB) TaqMan probes. One allelic probe was labeled with the FAM dye and the other with the fluorescent VIC dye. PCRs were conducted using TaqMan Universal Master Mix without UNG (Applied Biosystems) at 900 nM PCR primer concentrations and 200 nM TaqMan MGB-probe concentrations. The reactions were carried out in a 384-well format with a total reaction volume of 5 μl using 20 ng of genomic DNA. The plates were then placed in a thermal cycler (PE 9700, Applied Biosystems) and heated at 50°C for 2 min and 95°C for 10 min followed by 40 cycles of 95°C for 15 s and 60°C for 1 min. The TaqMan assay plates were transferred to a Prism 7900HT instrument (Applied Biosystems) in which the fluorescence intensity in each well of the plate was read.

Fluorescence data files from each plate were analyzed using automated software (SDS 2.1).

Statistical analysis

The $\chi 2$ tests were used to determine whether individual variants were in equilibrium at each locus in the population (Hardy–Weinberg equilibrium). Logistic regressions were used for calculating P values controlling for age, gender, and smoking status as covariates. P values and odds ratios (ORs) were obtained using logistic regression. Heterozygosity for each locus with allele frequencies p and q ($q = 1-p$) was derived using $H = 1-p2-q2 = 2p(1-p)$. We examined widely used measures of linkage disequilibrium (LD) between all pairs of biallelic loci; Lewontin's D' ($|D'|$) (Hedrick 1987) and r^2. Haplotypes and their frequencies were inferred using the algorithm developed by Stephens et al. (2001). Logistic regression analysis was used to calculate ORs, 95% confidential intervals (CIs), and corresponding P values after controlling for age, gender, and smoking status as covariates. Genotypes were given 0, 1, and 2 as codes in the additive model; 0, 1, and 1 in the dominant model; or 0, 0, and 1 in the recessive model, respectively. In the additive model, OR was expressed per number of rare alleles.

The effective number of independent marker loci in *TP53* was calculated to correct for multiple testing using the software SNPSpD (http://genepi.qimr.edu.au/general/daleN/SNPSpD/), which is based on the spectral decomposition (SpD) of matrices of pair-wise LD between SNPs (Nyholt 2004). The resulting number of independent marker loci was applied to correct for multiple testing. Statistical powers were calculated using Statistical Power Calculator (http://www.dssresearch.com/toolkit/spcalc/power_p2.asp).

Results

By direct DNA sequencing in 24 individuals, we identified 13 genetic variants with exons and flanking regions of *TP53*, including the promoter regions. Among 13 polymorphisms, five of the identified polymorphisms, including *−12256G>C, −11917G>A, −11849C>T, +441G>C*, and *+2486C>T*, were selected for larger-scale genotyping ($n = 595$) on the basis of locations, frequency (over 7.5%), LD, and haplotype tagging status (Table 2; Fig. 1). Genotype frequencies for cases and controls were in Hardy–Weinberg equilibrium. LD coefficients ($|D'|$) and r^2 among polymorphisms were also calculated (Fig. 1). All five SNPs were used for haplotype construction. Allelic frequencies of each polymorphism and haplotype were compared between patients and controls using logistic regression models (Table 3). Logistic regression analyses revealed that haplotype 3 (*−12256G, −11917G, −11849C, +441C,* and *+2486C*) of *TP53* showed marginal association with lung cancer risk in overall, male gender, and smoker groups; however, the association was lost after correction using SNPSpD. Other polymorphisms showed no association in overall analysis and all subgroup analyses. In the

Table 2 Frequencies of *TP53* polymorphisms in a Korean population

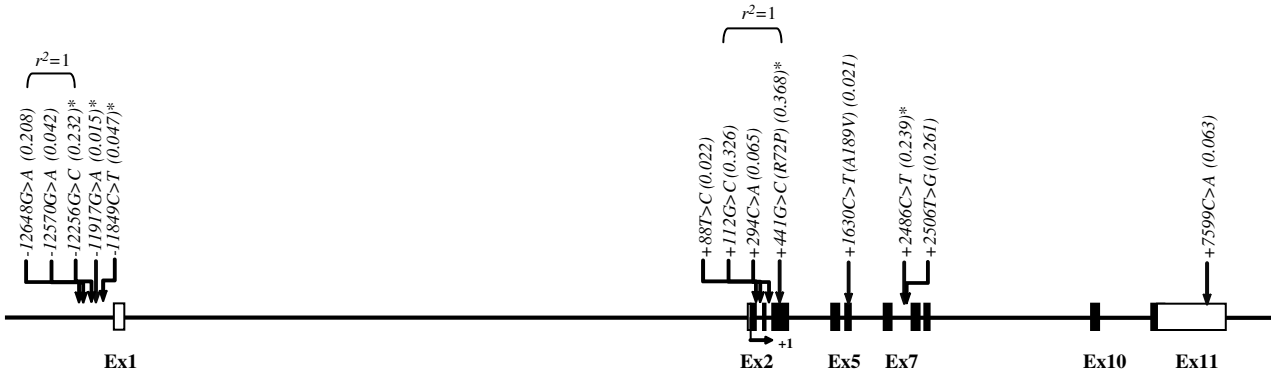
Loci	Position	Amino acid change	rs no.	Allele frequency	Heterozygosity	Hardy–Weinberg equilibrium[a]	
						Case	Control
−12648G>A	Promoter	–	rs2287498	0.208	0.330		0.999
−12570G>A	Promoter	–	Novel	0.042	0.080		0.978
−12256G > C	**Promoter**	**–**	**rs2287499**	**0.232**	**0.356**	**0.864**	**0.994**
−11917G > A	**Promoter**	**–**	**Novel**	**0.015**	**0.030**	**0.985**	**0.939**
−11849C > T	**Promoter**	**–**	**rs17806770**	**0.047**	**0.090**	**0.987**	**0.743**
+88T > C	Intron	–	Novel	0.022	0.043		0.994
+112G > C	Intron	–	rs1642785	0.326	0.440		0.914
+294C > A	Intron	–	Novel	0.065	0.122		0.946
+441G > C	**Exon 4**	**Arg72Pro**	**rs1042522**	**0.368**	**0.465**	**0.805**	**0.994**
+1630C > T	Exon 5	Ala189Val	Novel	0.021	0.041		0.995
+2486C > T	**Intron 7**	**–**	**rs12947788**	**0.270**	**0.394**	**0.643**	**1.000**
+2506T > G	Intron	–	rs12951053	0.261	0.386		0.895
+7599C > A	3′ UTR	–	novel	0.063	0.117		0.948

Bold data indicates single nucleotide polymorphisms genotyped in a larger population ($n = 595$); nonbold data based on the sequencing data ($n = 24$)

UTR untranslated region

[a] P values of deviation from lung cancer and normal subjects

A. Map of *TP53*(tumor protein p53 (LiFraumeni syndrome)) on chromosome 17p13.1 (19.2 Kb)



B. Haplotype of *TP53*

Hap.	-12256G>C	-11917G>A	-11849C>T	+441G>C	+2486C>T	Freq.
ht1	G	G	C	G	C	0.620
ht2	C	G	C	C	T	0.162
ht3	G	G	C	C	C	0.098
Others.	.	.	.	.	.	0.120

C. LDs among *TP53* polymorphisms

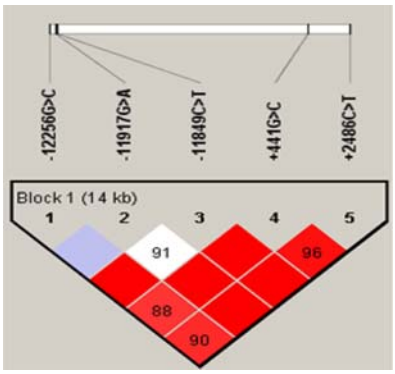


Fig. 1 Gene map, haplotypes, and linkage disequilibrium (LD) coefficients in *TP53*. **a** Gene map and single nucleotide polymorphisms (SNPs) in *TP53* on chromosome 17p13.1 (reference sequence of *TP53*: OMIM No. 191170). Coding exons are marked by *black blocks* and 5′ and 3′ untranslated regions (UTR) by *white blocks*. *Asterisks* indicate SNPs that were genotyped in a larger population. The frequencies of SNPs without larger-scale genotyping were based on sequencing data ($n = 24$). The first base of the translation site was denoted as nucleotide +1. **b** Haplotypes of *TP53*. Haplotypes with frequency >0.03 are presented. **c** LD coefficient ($|D'|$) among *TP53* SNPs. All five SNPs, *−12256G>C, −11917G>A, −11849C>T, +441G>C*, and *+2486C>T*, were used for haplotype construction. Others included CGTCT, GGCCT, CGCGC, GACCT, GGCGT, and CGCGT

stratified analyses by age, gender, and smoking status as well as analyses of historical types of lung cancer, no significant associations were found between *TP53* polymorphisms and lung cancer risk in a Korean population (Table 4).

Discussion

Based on the supposition that *TP53* polymorphisms are associated with lung cancer risk and that these polymorphisms may play a role as a predictor of lung cancer development, we conducted a preliminary study on *TP53* polymorphisms by sequencing at 24 samples and, for a further larger-scale study, selected five *TP53* polymorphisms via genotyping in a total of 595 samples, consisting of 299 lung patients and 296 controls. Our findings indicated no significant association between polymorphisms of the *TP53* gene and lung cancer risk in a Korean population. Considering the absence of association and the limitation of our study, the small number of study subjects might have affected the lack of association.

The tumor suppressor gene *TP53* encodes a transcription factor that is activated in response to antiproliferative functions such as cell-cycle arrest and apoptosis (Kastan et al. 1995). Inactivation of *TP53* by genetic alteration occurs frequently in a wide range of cancers (Soussi 2007). In particular, many groups have reported that the Arg72 and Pro72 variants of *TP53* (Arg72Pro) showed ethnic and functional differences (Petitjean et al. 2007). Furthermore, numerous studies analyzed the impact of these polymorphisms on cancer risk, but these findings have been inconsistent. Popanda et al. (2007) and Zhang et al. (2006) reported that *TP53* Arg72Pro polymorphism was significantly associated with susceptibility to lung cancer. In 2007, Mechanic et al. suggested that association with genetic variation in *TP53* and lung cancer risk was different depending on race (Mechanic et al. 2007). On the

Table 3 Logistic analysis of *TP53* polymorphisms with the risk of lung cancer while controlling for age, gender, and smoking status as covariates among lung cancer and normal subjects

Loci	Genotype	Case	Control	Codominant					Dominant					Recessive					Statistical power** (%)
				Crude OR (95% CI)	Crude *P*	Adjusted OR (95% CI)	*P*	P^{corr*}	Crude OR (95% CI)	Crude *P*	Adjusted OR (95% CI)	*P*	P^{corr*}	Crude OR (95% CI)	Crude *P*	Adjusted OR (95% CI)	*P*	P^{corr*}	
−12256G > C	G	169(0.61)	169(0.58)	0.92 (0.70 – 1.21)	0.56	0.87 (0.63–1.21)	0.42	NS	0.89 (0.64 – 1.24)	0.48	0.85 (0.57–1.27)	0.42	NS	0.99 (0.49 – 2.00)	0.97	0.84 (0.37–1.92)	0.68	NS	9.1
	CG	94(0.34)	107(0.37)																
	C	16(0.06)	17(0.06)																
−11917G > A	G	274(0.98)	280(0.96)	0.51 (0.19 – 1.38)	0.19	0.57 (0.18–1.82)	0.34	NS	0.51 (0.19 – 1.38)	0.19	0.57 (0.18–1.82)	0.34	NS	–	–	–	–	–	26.8
	AG	6(0.02)	12(0.04)																
	A	0(0.00)	0(0.00)																
−11849C > T	C	249(0.89)	271(0.92)	1.56 (0.89 – 2.73)	0.12	1.85 (0.93–3.68)	0.08	NS	1.53 (0.87 – 2.72)	0.14	1.85 (0.93–3.69)	0.08	NS	–	–	–	–	–	34.7
	CT	30(0.11)	22(0.08)																
	T	1(0.00)	0(0.00)																
+441G > C	G	108(0.39)	120(0.41)	1.11 (0.87 – 1.41)	0.41	1.11 (0.83–1.49)	0.47	NS	1.11 (0.79 – 1.54)	0.56	1.10 (0.73–1.65)	0.65	NS	1.22 (0.76 – 1.97)	0.41	1.25 (0.71–2.21)	0.44	NS	13.4
	CG	130(0.46)	136(0.46)																
	C	42(0.15)	37(0.13)																
+2486C > T	C	156(0.57)	146(0.50)	0.83 (0.64 – 1.08)	0.17	0.85 (0.63–1.16)	0.32	NS	0.76 (0.55 – 1.06)	0.11	0.81 (0.54–1.21)	0.30	NS	0.92 (0.50 – 1.70)	0.80	0.85 (0.41–1.75)	0.65	NS	28.6
	CT	96(0.35)	120(0.41)																
	T	21(0.08)	24(0.08)																
ht1	−/−	46(0.17)	46(0.16)	0.98 (0.78 – 1.24)	0.88	1.02 (0.77–1.35)	0.91	NS	0.93 (0.60 – 1.46)	0.77	0.96 (0.57–1.64)	0.89	NS	1.00 (0.71 – 1.41)	0.99	1.06 (0.70–1.60)	0.79	NS	8.1
	−/ht1	122(0.45)	132(0.46)																
	ht1/ht1	105(0.38)	111(0.38)																
ht2	−/−	195(0.71)	195(0.67)	0.84 (0.62 – 1.15)	0.28	0.79 (0.55–1.15)	0.22	NS	0.83 (0.58 – 1.19)	0.31	0.80 (0.52–1.23)	0.30	NS	0.73 (0.28 – 1.96)	0.54	0.54 (0.17–1.75)	0.31	NS	19.1
	−/ht2	71(0.26)	84(0.29)																
	ht2/ht2	7(0.03)	10(0.03)																
ht3	−/−	**209(0.77)**	**247(0.85)**	**1.63 (1.11 – 2.40)**	**0.01**	1.55 (0.98–2.46)	0.06	NS	**1.80 (1.17 – 2.77)**	**0.007**	1.74 (1.05–2.89)	0.03	NS	1.33 (0.35 – 5.00)	0.67	0.70 (0.11–4.58)	0.71	NS	59.8
	–/ht3	**59(0.22)**	**38(0.13)**																
	ht3/ht3	**5(0.02)**	**4(0.01)**																

Logistic regression models were used for calculating odds ratios (OR) [95% confidential interval (CI)] and corresponding *P* values for each single nucleotide polymorphism (SNP) site and haplotype. Results of codominant, dominant, and recessive models are also given. Bold data indicate *P* values < 0.05

NS not significant

* To achieve the optimal correction for multiple testing of SNPs in linkage disequilibrium (LD) with each other, the effective number of independent marker loci (4.1535) in *TP53* was calculated using the software SNPSpD (http://genepi.qimr.edu.au/general/daleN/SNPSpD/) on the basis of the spectral decomposition (SpD) of matrices of pair-wise LD between SNPs (Nyholt 2004)

** Statistical powers were calculated using Statistical Power Calculator (http://www.dssresearch.com/toolkit/spcalc/power_p2.asp). Two-tailed test of allele frequency in case and control as well as 5% of alpha error level were used

Table 4 Logistic analysis of *TP53* haplotype-3 with the risk of lung cancer in a subgroup of Korean population controlling for age, gender, and smoking status as covariates among lung cancer patients and normal subjects

Subgroups	Genotype	Case	Control	Analyzing models referent			Codominant			Dominant			Recessive		
				OR (95% CI)	P	P^{corr}	OR (95% CI)	P	P^{corr}	OR (95% CI)	P	P^{corr}	OR (95% CI)	P	P^{corr}
Male	–/–	153(0.77%)	236(0.86%)	1											
	–/ht3	45(0.23%)	33(0.12%)	**1.93(1.12–3.32)**	**0.02**	NS	1.55(0.96–2.49)	0.07	NS	**1.79(1.06–3.03)**	**0.03**	NS	0.44(0.05–4.24)	0.48	NS
	ht3/ht3	1(0.01%)	4(0.01%)	0.71(0.23–2.22)	0.56	NS									
Female	–/–	56(0.76%)	11(0.69%)	1											
	–/ht3	14(0.19%)	5(0.31%)	8.45(0.12–619.82)	0.33	NS	8.45(0.12–619.82)	0.33	NS	8.45(0.12–619.82)	0.33	NS	–	–	–
	ht3/ht3	4(0.05%)	0(0.00%)	–	–										
Smoker	–/–	151(0.76%)	169(0.85%)	1											
	–/ht3	44(0.22%)	26(0.13%)	**2.03(1.15–3.57)**	**0.01**	NS	1.59(0.98–2.60)	0.06	NS	**1.86(1.08–3.22)**	**0.03**	NS	0.45(0.05–4.32)	0.49	NS
	ht3/ht3	3(0.02%)	4(0.02%)	0.72(0.23–2.23)	0.57	NS									
Nonsmoker	–/–	58(0.77%)	78(0.87%)	1											
	–/ht3	15(0.20%)	12(0.13%)	1.16(0.26–5.13)	0.85	NS	1.20(0.28–5.10)	0.81	NS	1.18(0.27–5.18)	0.83	NS	–	–	–
	ht3/ht3	2(0.03%)	0(0.00%)	–	0.99	NS									
Cell type															
Adenocarcinoma	–/–	81(72.3%)	247(85.5%)	1											
	–/ht3	28(25.0%)	38(13.2%)	**2.44(1.21–4.92)**	**0.01**	**0.05**	**2.18 (1.18–4.00)**	**0.01**	**0.05**	**2.46 (1.24–4.87)**	**0.01**	**0.04**	2.06 (0.21–19.9)	0.53	NS
	ht3/ht3	3(2.7%)	4(1.4%)	1.13(1.09–1.18)	0.41	NS									
Squamous-carcinoma	–/–	65(81.3%)	247(85.5%)	1											
	–/ht3	15(18.8%)	38(13.2%)	1.12(0.65–2.98)	0.403	NS	1.18 (0.58–2.39)	0.64	NS	1.30 (0.61–2.76)	0.50	NS	–	–	–
	ht3/ht3	0(0.0%)	4(1.4%)	–	–	NS									

Logistic regression models were used for calculating odds ratios (OR) [95% confidential interval (CI)] and corresponding *P* values for each single nucleotide polymorphism (SNP) site and haplotype. Results of referent, codominant, dominant, and recessive models are also given. Bold data indicate *P* values < 0.05

To achieve the optimal correction for multiple testing of SNPs in linkage disequilibrium (LD) with each other, the effective number of independent marker loci (4.1535) in *TP53* was calculated using the software SNPSpD (http://genepi.qimr.edu.au/general/daleN/SNPSpD/) on the basis of the spectral decomposition (SpD) of matrices of pair-wise LD between SNPs (Nyholt 2004)

NS not significant

other hand, others could not find such association (Jin et al. 1995; Matakidou et al. 2003): Pierce et al. reported no significant association between the *TP53* codon 72 polymorphisms and lung cancer (Pierce et al. 2000), and de las Penas et al. (2006) also suggested no association between *TP53* polymorphisms and survival of patients with chemotherapy-treated non-small-cell lung cancer. Our data revealed that haplotype 3 (−12256G, −11917G, −11849C, +441C, +2486C) of *TP53* showed marginal association with the lung cancer risk in overall, male gender, smokers, and adenocarcinoma cell types, but the association was lost after correction using SNPSpD. Therefore, our data was consistent with these studies, demonstrating no significant association with *TP53* Arg72Pro and risk of lung cancer. In summary, 13 sequence variants of *TP53* were identified in 24 Korean individuals through direct sequencing. We selected five of these polymorphisms for larger-scale genotyping ($n = 595$) and observed no significant difference in allele genotype distribution between lung cancer patients and controls. Thus, we concluded that no significant association exists between these *TP53* polymorphisms, including *TP53* Arg72Pro, and lung cancer risk in a Korean population.

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