RESEARCH COMMUNICATION

APEX1 Asp148Glu Gene Polymorphism is a Risk Factor for Lung Cancer in Relation to Smoking in Japanese

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Abstract

DNA repair enzymes play an important role in the development of various kinds of cancer. We here analyzed associations of XPD Lys751Gln, APEX1 Asp148Glu, XRCC1 Arg399Gln, and XRCC3 Thr241Met gene polymorphisms in DNA repair pathways in relation to the risk of lung cancer using PCR-RFLP. The study involved 104 lung cancer patients and 120 non-cancer controls divided into non-smokers and smokers. We found a statistically significant interaction between APEX1 Asp148Glu and the risk for lung cancer (adjusted OR 2.78, 95% CI 1.58-4.90, p=0.0004), of both adenocarcinoma (adjusted OR 2.24, 95%CI 1.18-4.25, p=0.014) and squamous cell carcinoma (adjusted OR 4.75, 95%CI 1.79-12.60, p=0.002) types. XRCC1 Arg399Gln showed a borderline significant association with adenocarcinoma (adjusted OR 1.89, 95%CI 1.00-3.57, p=0.051). The combined effect of smoking and presence of the APEX1 Asp148Glu demonstrated a significant association with risk of lung cancer (adjusted OR 3.61, 95% CI 1.74-7.50, p = 0.001). The XPD Lys751Gln and XRCC3 Thr241Met genotypes displayed no statistically significant risk. Our findings suggest that the APEX1 Asp148Glu is associated with increased risk for primary lung cancer in Japanese individuals partaking in smoking.

Keywords: Gene polymorphisms - lung cancer - smoking - APEX1

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Introduction

Lung cancer is the most common cancer in the world (Edwards et al., 2005), and it is caused by a complex combination of genetic and environmental carcinogenic factors such as tobacco smoke.

Tobacco smoke contains many chemical carcinogens and reactive oxygen species, including polycyclic aromatic hydrocarbons. DNA damage induced by these carcinogens or by endogenous metabolic processes can be manifested as gene mutations. Recently, we reported that genetic polymorphisms of NAT2 and CYP1A2 in metabolic processes contributed to lung cancer susceptibility dependent on smoking status (Osawa et al., 2007).

The DNA repair pathways, including nucleotide excision repair (NER), base excision repair (BER) and double-strand break repair (DSBR) play an important role in repairing the DNA damage resulting from chemical alterations of a single base, such as methylated, oxidized, or reduced bases (Yu et al., 1999; Wood et al., 2001). In the NER pathway, the xeroderma pigmentosum group D/ excision repair cross-complementing group 2 (XPD/ ERCC2) protein is an evolutionarily conserved helicase, a subunit of transcription factor II H (Schaeffer et al., 1994). The variant alleles Asp312Asn and Lys751Gln in XPD have been associated with relatively high risks of lung cancer in Caucasian population (Manuguerra et al., 2006; Zienolddiny et al., 2006), but a recent study concluded that the XPD Lys751Gln are associated with a statistically significant lung cancer risk than Asp312Asn in the Chinese population (Yin et al., 2007). There are four key proteins in the BER pathway: 8-oxoguanine DNA glycosylase (OGG1), Mut Y homolog (MUTYH/MYH), Apurinic/apyrimidinic endonuclease-1(APEX1/APE1), and X-ray cross-complementing group 1(XRCC1). We also reported that genetic polymorphisms of MUTYH Gln324His, but not OGG1 Ser326Cys, contributed to lung cancer susceptibility depending on the smoking status of individuals within the Japanese population (Miyaishi et al., 2009). The most stable product of oxidative DNA damage, APEX1 exhibits 3'-phosphodiesterase activity that removes the abasic sites from cleaved DNA by OGG1 and MUTYH proteins (Bennett et al, 1997). XRCC1 acts as a scaffold for other proteins, such as DNA polymerase β, ligase III, and ADP-ribose polymerase, in the gap-filling step (Caldecott et al., 1996). The association between the APEX1 Asp148Glu or XRCC1 Arg399Gln polymorphisms and lung cancer risk has been evaluated in a number of

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epidemiological studies (Ito et al. 2004; Hung et al., 2005; De Ruyck et al., 2007). A recent meta-analysis showed that the XRCC1 399Gln/Gln genotype was associated with an increased risk of lung cancer among Asians but not among Caucasians (Kiyohara et al., 2006). In the DSBR pathway, X-ray repair cross-complementing groups 3 (XRCC3) participates in DNA double-strand break/recombination repair and likely participates (Tebbs et al., 1995). There are several reports that the Thr241Met polymorphism of XRCC3 and lung cancer risk was associated in Caucasian population (López-Cima et al., 2007; Improta et al., 2008). To our knowledge, few previous studies have examined the effect of these polymorphisms on the association between smoking and lung cancer in Japanese population.

In this study, we focused on XPD Lys751Gln (rs13181), APEX1 Asp148Glu (rs1130409), XRCC1 Arg399Gln (rs25487) and XRCC3 Thr241Met (rs861539) with respect to exposure to tobacco smoke to examine if genetic polymorphisms in DNA repair genes were implicated in NER, BER and DSBR pathways and were also associated with the risk of developing lung cancer.

Materials and Methods

Study Subjects

The 104 lung cancer patients (68 with lung adenocarcinoma, 31 with lung squamous cell carcinoma, 5 with other carcinomas) were included in a previous study that investigated the genetic polymorphisms of metabolic enzymes, which were recruited between April 2001 and July 2002 at the Hyogo Cancer Center. The 120 control individuals were without cancer and had visited local medical clinics between November 2002 and March 2003 (Osawa et al., 2007; Miyaishi et al., 2009). Informed consent was obtained and detailed exposure data on smoking was collected by personal interview. The study design was approved by the Ethics Review Committee on Genetic and Genomic Research, Kobe University Graduate School of Medicine. Informed consent was obtained from all patients and controls, and all samples were coded after collection of blood and smoking frequency data. The amount of smoke exposure was calculated as pack-years, the product of the number of years an individual smoked and the average number of cigarettes smoked per day (converted into a standard pack of 20 cigarettes).

Genotyping

The genomic DNA to be used was isolated in a previous study (Osawa et al., 2007). The genotypes of XPD Lys751Gln , APEX1 Asp148Glu, XRCC1 Arg399Gln and XRCC3 Thr241Met were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis, as described previously (Duell et al., 2000; Hu et al., 2001).

Statistical Analysis

Statistical analysis was performed with the PASW software package (version 17.0 for Windows; SPSS Japan Inc., Tokyo, Japan). The Hardy-Weinberg equilibrium assumption was assessed in the control sample using a goodness-of-fit chi-square test. The crude and adjusted odds ratio (OR) and the corresponding 95% confidence intervals (CI) were determined through unconditional multiple logistic regression. A P-value less than 0.05 was considered statistically significant. The association of combined genotypes was assessed by logistic regression analysis. ORs, which were computed to estimate the association between certain genotypes and lung cancer, were adjusted for age, gender and smoking habit. The subjects were divided into two groups according to pack-years of smoking: non-smokers (pack-years=0) and habitual smokers (pack-years >0).

Results

Characteristics in case and control subjects

We present the characteristics of lung cancer in Table 1, including 104 patients and 120 controls. There was no difference in the gender distribution (p = 0.408) between males (patients, 66.3%; controls, 60.8%) and females (patients, 33.7%; controls, 39.2%). There was no difference in the average age (± SD) between patients (66.3±9.3 years) and controls (67.3±6.6 years; p=0.358). There was also no difference in the average pack-years (± SD) between patients (34.7±31.9) and controls (26.1±35.4; p=0.064). Histological analysis of samples from patients found that 65.4% had adenocarcinoma, 29.8% had squamous cell carcinoma and other types of carcinoma were in the remaining 4.8%.

Genotype distribution of lung cancer

Genotyping results of XPD Lys751Gln, APEX1 Asp148Glu, XRCC1 Arg399Gln and XRCC3 Thr241Met adjusted for gender, age, and smoking habit along with

Table 1. Characteristics of Lung Cancer Case and Control Subjects

Itme	Patients		Controls		P-value
	n	%	n	%	
Number	104		120		
Gender					
males	69	66.3	73	60.8	0.408[a]
females	35	33.7	47	39.2	
Age					
~64	35	33.7	51	42.5	
65~69	17	16.3	28	23.3	
70~74	33	31.7	20	16.7	
74~	19	18.3	21	17.5	
Mean±S.D.	66.3±9.3		67.3±6.6		0.358[b]
Smoking status					
never (pack-years=0)	31	29.8	54	45.0	
ever (pack-years>0)	72	69.2	61	50.8	
unknown	1	1.0	5	4.2	
Mean±S.D.	34.7±31.9		26.1±35.4		0.064[b]
Histological type					
adenocarcinoma	68	65.4			
SCC	31	29.8			
others	5	4.8			

a: X^2 analysis; b: Student' s T; SCC, squamous cell carcinoma

Table 2. Genotype Distribution in Lung Cancer and Allele Frequency

Genotype	patients n	controls n	crude OR (95%CI)	P-value	adjusted OR (95%CI)[a]	P-value	Allele frequency	patients %	controls %
XPD									
Gln/Gln	95	113	1.00		1.00		Gln	95.7	97.1
Gln/Lys, Lys/ Lys	9	7	1.53 (0.55-4.26)	0.416	1.50(0.53-4.29)	0.445	Lys	4.3	2.9
APEX1									
Asp/Asp	41	72	1.00		1.00		Asp	64.4	75.8
Asp/Glu, Glu/ Glu	63	48	2.31(1.35-3.94)	0.002	2.78(1.58-4.90)	0.0004	Glu	35.6	24.2
XPCC1									
Arg/ Arg	47	61	1.00		1.00		Arg	69.2	70.4
Arg/Gln, Gln/Gln	57	59	1.25(0.74-2.12)	0.400	1.32(0.77-2.28)	0.314	Gln	30.8	29.6
XRCC3									
Thr/ Thr	92	98	1.00		1.00		Thr	94.2	89.6
Thr/Met, Met/ Met	12	22	0.58(0.27-1.24)	0.161	0.67(0.31-1.46)	0.313	Met	5.8	10.4

a: OR adjusted for gender, age, smoking habit

allele frequencies are shown in Table 2. The allele frequencies of the four gene polymorphisms in controls were consistent with the Hardy-Weinberg equilibrium. The adjusted ORs for the XPD Gln/Lys and Lys/Lys genotypes compared with the Gln/Gln genotype showed no statistically significant risk for lung cancer (crude OR 1.53, 95% CI 0.55-4.26, p=0.416; adjusted OR 1.50, 95% CI 0.53-4.29, p=0.445). The OR for the APEX1 Asp/Glu and Glu/Glu genotypes compared with Asp/Asp genotype showed a increased risk for development of lung cancer (crude OR 2.31, 95% CI 1.35-3.94, p=0.002; adjusted OR 2.78, 95% CI 1.58-4.90, p=0.0004). The ORs for the XRCC1Arg/Gln and Gln/Gln genotypes compared with the Arg/Arg genotype showed no statistically significant risk for lung cancer (crude OR 1.25, 95% CI 0.74-2.12, p=0.400; adjusted OR 1.32, 95% CI 0.77-2.28, p=0.314). The ORs for the XPCC3 Thr/Met and Met/Met genotypes compared with the Thr/Thr genotype showed no statistically significant risk for lung cancer (crude OR 0.58, 95% CI 0.27-1.24, p=0.161; adjusted OR 0.67, 95% CI 0.31-1.46, p=0.313). These results indicated that APEX1 Asp148Glu polymorphism may have a significant effect with respect to development of lung cancer in the four gene polymorphisms.

Genotype distribution in histological type of lung cancer

Table 3 summarizes the genotype distribution for lung adenocarcinoma and squamous cell carcinomas, showing the OR adjusted for gender, age and smoking habits. The adjusted ORs for the XPD Gln/Lys and Lys/Lys genotypes compared with the Gln/Gln genotype showed no statistically significant risk for either adenocarcinoma or squamous cell carcinoma (OR 1.62, 95%CI 0.50–5.23, p=0.420 for adenocarcinoma; OR 1.20, 95%CI 0.24–6.04, p=0.828 for squamous cell carcinoma).The OR for the APEX1 Asp/Glu and Glu/Glu genotypes were statistically

Table 3. Genotype Distribution in Relation to Histological Type in Lung Cancers

Genotype	Adenocarcinoma						Squamous Cell Carcinoma					
	patients n	controls n	crude OR (95%CI)	P-value	adjusted OR (95%CI)[a]	P-value	patients n	controls n	crude OR (95%CI)	P-value	adjusted OR (95%CI)[a]	P-value
XPD												
Gln/Gln	62	113	1.00		1.00		28	113	1.00		1.00	
Gln/Lys, Lys/ Lys	6	7	1.56 (0.50-4.85)	0.441	1.62 (0.50-5.23)	0.420	3	7	1.73 (0.42-7.12)	0.448	1.20 (0.24-6.04)	0.828
APEX1												
Asp/Asp	28	72	1.00		1.00		12	72	1.00		1.00	
Asp/Glu, Glu/ Glu	40	48	2.14 (1.17-3.93)	0.014	2.24 (1.18-4.25)	0.014	19	48	2.38 (1.06-5.34)	0.036	4.75 (1.79-12.60)	0.002
XPCC1												
Arg/ Arg	27	61	1.00		1.00		18	61	1.00		1.00	
Arg/Gln, Gln/Gln	41	59	1.57 (0.86-2.87)	0.143	1.89 (1.00-3.57)	0.051	13	59	0.75 (0.34-1.66)	0.473	0.66 (0.27-1.58)	0.347
XRCC3												
Thr/ Thr	60	98	1.00		1.00		28	98	1.00		1.00	
Thr/Met, Met/ Met	8	22	0.59 (0.25-1.42)	0.241	0.67 (0.27-1.65)	0.383	3	22	0.48 (0.13-1.71)	0.256	0.56 (0.14-2.28)	0.421

a: OR adjusted for gender, age, smoking habit

Table 4. Genotype Distribution in Relation to Smoking Status in Lung Cancers

Genotype	Non-smokers (pack-years=0)						Smokers (pack-years>0)					
	patients n	controls n	crude OR (95%CI)	P-value	adjusted OR (95%CI)[a]	P-value	patients n	controls n	crude OR (95%CI)	P-value	adjusted OR (95%CI)[a]	P-value
XPD												
Gln/Gln	28	52	1.00		1.00		66	56	1.00		1.00	
Gln/Lys,	3	2	2.79	0.277	2.57	0.356	6	5	1.02	0.977	1.02	0.976
Lys/ Lys			(0.44-17.67)		(0.35-18.94)				(0.30-3.52)		(0.29-3.56)	
APEX1												
Asp/Asp	11	28	1.00		1.00		30	44	1.00		1.00	
Asp/Glu,	20	26	1.96	0.147	1.67	0.289	42	17	3.62	0.001	3.61	0.001
Glu/ Glu			(0.79-4.86)		(0.65-4.32)				(1.75-7.52)		(1.74-7.50)	
XPCC1												
Arg/ Arg	12	29	1.00		1.00		35	30	1.00		1.00	
Arg/Gln,	19	25	1.84	0.185	2.37	0.083	37	31	1.02	0.948	1.01	0.971
Gln/Gln			(0.75-4.51)		(0.89-6.26)				(0.52-2.02)		(0.51-2.01)	
XRCC3												
Thr/ Thr	28	42	1.00		1.00		63	53	1.00		1.00	
Thr/Met,	3	12	0.38	0.155	0.37	0.160	9	8	0.95	0.916	0.92	0.877
Met/ Met			(0.10-1.45)		(0.09-1.48)				(0.34-2.63)		(0.33-2.59)	

a: OR adjusted for gender, age

significant for both adenocarcinoma (crude OR 2.14, 95% CI 1.17-3.93, p=0.014; adjusted OR 2.24, 95% CI 1.18-4.25, p=0.014) and squamous cell carcinoma (crude OR 2.38, 95% CI 1.06-5.34, p=0.036; adjusted OR 4.75, 95% CI 1.79-12.60, p=0.002) compared with the Asp/Asp genotype. The ORs for the XRCC1Arg/Gln and Gln/Gln genotypes compared with the Arg/Arg genotype was a borderline significant for adenocarcinoma (crude OR 1.57, 95% CI 0.86-2.87, p=0.143; adjusted OR 1.89, 95% CI 1.00-3.57, p=0.051), whereas that not for squamous cell carcinoma (crude OR 0.75, 95% CI 0.34-1.66, p=0.473; adjusted OR 0.66, 95% CI 0.27-1.58, p=0.347). The adjusted ORs for the XPCC3 Thr/Met and Met/Met genotypes compared with the Thr/Thr genotype showed no statistically significant risk for either adenocarcinoma or squamous cell carcinoma (OR 0.67, 95%CI 0.27–1.65, p=0.383 for adenocarcinoma; OR 0.56, 95%CI 0.14–2.28, p=0.421 for squamous cell carcinoma). Therefore, the study of cancer by histological type indicated that APEX1 Asp148Glu polymorphism was associated with a risk for development of lung cancer.

Genotype distribution in smoking status

The combined effect of smoking and the four polymorphisms, adjusted for gender and age, are shown in Table 4. The adjusted ORs for the XPD Gln/Lys and Lys/Lys genotypes compared with the Gln/Gln genotype showed no statistically significant risk in non-smokers and smokers (OR 2.57, 95%CI 0.35-18.94, p=0.356 in non-smokers; OR 1.02, 95%CI 0.29-3.56, p=0.976 in smokers). The ORs for the APEX1 Asp/Glu and Glu/Glu genotypes compared with the Asp/Asp genotype in smokers was significantly increased (crude OR 3.62, 95%CI 1.75-7.52, p=0.001; adjusted OR 3.61, 95%CI 1.74-7.50, p=0.001), whereas that not in non-smokers (crude OR 1.96, 95%CI 0.79-4.86, p=0.147; adjusted OR 1.67, 95%CI 0.65-4.32, p=0.289). The adjusted ORs for the XRCC1 Arg/Gln and Gln/Gln genotypes compared with the Arg/Arg genotype were not statistically significant (OR 2.37, 95%CI 0.89-6.26, p=0.083 in non-smokers; OR 1.01, 95%CI 0.51-2.01, p=0.971 in smokers). The adjusted ORs for the XRCC1 Arg/Gln and Gln/Gln genotypes compared with the Arg/Arg genotype were not statistically significant (OR 0.37, 95%CI 0.09-1.48, p=0.160 in non-smokers; OR 0.92, 95%CI 0.33-2.59, p=0.877 in smokers). These results indicate that the APEX Asp148Glu polymorphism have statistically a significant risk of lung cancer according to smoking.

Discussion

We attempted to analyze the association among and between XPD Lys751Gln, APEX1 Asp148Glu, XRCC1 Arg399Gln and XRCC3 Thr241Met gene polymorphisms. Our results support that polymorphisms in two BER genes increased the risk of developing lung cancer (APEX1 Asp148Glu) or tend to increase the risk of lung adenocarcinoma (XRCC1 Arg399Gln). On the other hand, no association was found between two genes that participate in the NER and DSBR repair processes (XPD Lys751Gln and XRCC3 Thr241Met) and the risk of lung cancer. In particular, we found a strong statistically significant interaction between APEX1 Asp148Glu and smoking. This polymorphism was located within the endonuclease domain of the protein (Walker et al., 1993), but it did not reduce endonuclease activity (Hadi et al., 2000). Instead it may lead to a reduced ability to communicate with other BER proteins, in turn leading to reduced repair efficiency, and a possibility that the Glu allele may have higher sensitivity to ionizing radiation (Hu et al., 2001). A recent study reported an association between the APEX1 148Glu allele and increased risk in the development of lung cancer among light, current Japanese smokers (Ito et al., 2004). Our findings are consistent with these previous studies and suggest that APEX1 variation may also play a role in predisposition to lung cancer.

For XRCC1 Arg399Gln variants, we found a tendency to increase on lung adenocarcinoma cancer risk. The XRCC1 Arg399Gln has associated with higher mutagen sensitivity and higher levels of DNA adducts (Matullo et al., 2001). It has previously reported to have an important genetic determinant of squamous cell carcinoma of the lung (Park et al., 2002) or adenocarcinoma (Divine et al., 2001). It was also reported that XRCC1 Arg399Gln might be prognostic factors in non-smoking female patients with lung adenocarcinoma (Yin et al., 2009). It may be attributable to differences in the carcinogenesis pathways among the histological types of lung cancer.

The XPD Lys751Gln have been observed a lower DNA repair capacity for UV-induced DNA damage in XPD 751Gln alleles (Qiao et al., 2002). The recent meta-analysis revealed an association between lung cancer and the XPD 751Gln alleles (Vineis et al., 2009). Our results didn't confirm an association between these polymorphisms and the risk of lung cancer. XRCC3 Thr241Met also was not associated with individual susceptibility for lung cancer in this study. The XRCC3 241Met allele has previously been associated with less efficient DNA repair and eliminated aberrant cells with mitotic defects (Matullo et al., 2001; Lindh et al., 2006). However, several studies have also been shown to explain the lack of association between XRCC3 Thr241Met and lung cancer risk in Caucasian population (David-Beabes et al., 2001; Misra et al., 2003). Our data may be biased by the relatively small number as a hospital-based case-control study, because we have several limitations. Therefore, we would require further verification as predictive biomarkers in a larger study population and need to clarify the gene-environment interaction between smoking and these genotypes.

In conclusion, we analyzed the association between XPD, APEX1, XRCC1, and XRCC3 polymorphisms and individual susceptibility for development of lung cancer in the Japanese population. Our results suggest that APEX1 Asp148Glu gene polymorphism appear to play an important role in modifying the risk for development lung cancer in the Japanese population. APEX1 Asp148Glu gene polymorphism may be useful markers of genetic susceptibility to lung cancer, and require further verification as predictive biomarkers in a larger population study.

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