Association between genetic polymorphisms of *CYP2A13*, *CYP2A6* and risk of nasopharyngeal carcinoma in southern Chinese population

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Abstract: Background: Cytochrome P450 2A13 (CYP2A13) and 2A6 (CYP2A6) are enzymes expressed in the human respiratory tract, exhibit high efficiency in the metabolic activation of tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). A C→T transition in the *CYP2A13* gene causes Arg257Cys amino acid substitution and a deletion of the *CYP2A6* gene named as *CYP2A6 *4*, both of them result in a significantly reduced activity toward NNK and other substrates. In this case-control study, we investigated the association between the *CYP2A13* and *CYP2A6* variants, smoking status and the risk of developing nasopharyngeal carcinoma (NPC) in the Cantonese population living in southern China. **Materials and Methods:** Genotypes of *CYP2A13* and *CYP2A6* genes were analyzed by using polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP) assays and two-step PCR method. **Results:** Neither the *CYP2A13* -3375*T* variants nor *CYP2A6 *4* variants were associated with risk of NPC (OR = 0.84, 95% CI = 0.59–1.20, and OR = 0.83, 95% CI = 0.58–1.18, respectively) compared with their wild genotypes. Combination analysis showed that individuals with both *CYP2A13 CT* or *TT* variants and *CYP2A6 *4* variants had no association with risk for NPC (OR = 0.71, 95% CI = 0.33–1.52) compared with those with both *CYP2A13 CC* and *CYP2A6 *1/*1* genotypes. No association with the risk of NPC was observed in smokers with *CYP2A13 C/T* polymorphisms or smokers with *CYP2A6 *4* variant polymorphisms (OR = 0.75, 95% CI = 0.43–1.32, and OR = 0.90, 95% CI = 0.27–1.70; respectively), including after stratification of smoking status. Furthermore, we did not observe association between the combination of two gene polymorphisms and smokers and risk of developing NPC, including the stratification of smoking. **Discussions:** Based on the results of this study, the effect of these two CYP2A13 and CYP2A6 enzymes may be not so important in developing of NPC as in other cancers, such as lung cancer.

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Introduction

Nasopharyngeal carcinoma (NPC) is rare in most countries and the incidence belows 1/100,000 (Yu and Yuan, 2002). However, it is one of the most common cancers in southern China including Guangdong, Guangxi and Hunan (Yu and Yuan, 2002). The distinct geographical distribution of NPC seems to be related with certain environmental and hereditary factors. Epstein-Barr virus (EBV) is one of the environmental risk factors which is widely recognized to involve in the carcinogenesis of NPC, because of the detection of EBV genomes in NPC tumor cells (Vasef MA, 1997) and elevated serum levels of IgA and IgG antibodies to EBV in NPC patients (Zong YS, 1992). The preserved foods, such as salted fish, plum vegetable and fermented eggs are considered as etiological factors for NPC, since epidemiological studies have confirmed high levels of nitrosamine from these foods (Hildesheim, 1993; Yu, 1989). In addition, tobacco smoke is also recognized as consensus risk factor for NPC, through previous studies on the association between smoking and NPC in NPC-endemic areas (Nam, 1992; Vaughan, 1996; Cheng, 1999). Other environmental factors include wood dust, formaldehyde and kitchen smog (Hildesheim, 2001).

Although many environmental factors were associated with NPC, only a few people develop the disease in areas where NPC is endemic, suggesting that genetic difference such as single nucleotide polymorphisms (SNP) may contribute to NPC carcinogenesis. There is accumulating evidence of association between genetic polymorphism in NPC susceptibility. Polymorphisms in human leukocyte antigen (HLA) class Ⅰ and Ⅱ alleles (Hildesheim, 2002), glutathione S-transferase M1 (GSTM1) (Guo,

2008), homozygous for an allele (c2 allele) of the CYP2E1 (Hildesheim, 1997) and X-ray repair cross-complementing group 1 (XRCC1) (Cao, 2006) have been reported with association with NPC susceptibility.

CYP2A13, one of the three members of the human CYP2A enzyme family, is expressed predominantly in the respiratory tract with the highest level observed in the nasal mucosa (Su, 2000). CYP2A6, another member of the CYP2A enzyme family, has also been detected in human nasal mucosa (Su, 1996). Both of these two enzymes are highly active in the metabolic activation of a major tobacco-specific carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (Su, 2000; Su, 1996). Recently, a 3375C→T variation in exon 5 of *CYP2A13* gene has been identified, and this single nucleotide polymorphism leads to an Arg257Cys amino acid change (Zhang, 2002), and a deletion of the *CYP2A6* gene named as *CYP2A6 *4*, which results in the absence of CYP2A6 protein, has been discovered in a Japanese population (Kamataki, 1999). Functional analysis showed that 3375C→T variation (Zhang, 2002) and deletion of *CYP2A6* (Kamataki, 1999) have significantly reduced their catalytic activity toward NNK and other substrates compared with their wild genotypes. Recently, the relationship between genetic polymorphisms of *CYP2A13* and several cancers, including lung cancer (Wang, 2003; Cauffiez, 2004) and bladder cancer (Song, 2009), have been investigated in several ethnic groups. Polymorphisms of *CYP2A6* also have been studied in lung cancer (Wang, 2003; Miyamoto, 1999) and esophageal cancer (Sepehr, 2004). In this retrospective case-control study, we investigated the association between the *CYP2A13* and *CYP2A6* variants, smoking status and the risk of developing NPC in the Cantonese population living in southern China.

Materials and Methods

Patients and samples

The study group consisted of 437 patients with histopathologically confirmed, untreated NPC and 470 cancer-free controls. The NPC patients were consecutively recruited from February 2001 to September 2003 at Sun Yat-sen University Cancer Center. Disease staging was performed in accordance with the Chinese 1992 TNM staging system (Min, 1994). Population controls were selected from a community screening program for early detection of cancer. For each eligible case, we tried to match one control subject by sex, age (± 5 years) and ethnicity (Cantonese). At recruitment, informed consent was obtained from each subject, and each participant was then interviewed to solicit detailed information on demographic characteristics and lifetime history of tobacco use. Overall, 500 eligible cases and 500 eligible controls agreed to further risk factor interviews administered by a trained nurse-interviewer, with the final study consisting of 437 cases (87.4%) and 470 controls (94.0%) due to lack of information on smoking or inability to collect blood from some subjects. Information was collected on the number of cigarettes smoked per day, the age at which the subjects started smoking, and the age at which ex-smokers stopped smoking. Smokers were considered current smokers if they had smoked up to 1 year before the date of cancer diagnosis (or up to the date of the interview for controls). This study was approved by the Hospital Review Board of Sun Yat-sen University Cancer Center.

CYP2A13 and *CYP2A6* genotyping

DNA was extracted from peripheral blood cells by using DNA Blood Mini Kit (Qiagen, Hilden, Germany). Genotypes of *CYP2A13* and *CYP2A6* genes were analyzed by using PCR-RFLP assays and two-step PCR method as described previously (Wang, 2003).

To ensure quality control, genotyping was performed with blinding to case/control status, and a 15% masked, random samples of cases (n = 66) and controls (n = 71) was tested twice by different persons, and the results were concordant for all masked duplicate sets.

Statistical analysis

The Hardy-Weinberg Equilibrium was tested to compare the observed and expected genotype frequencies among cases and controls, respectively. χ^2 tests were used to examine the differences in genotype distributions between cases and controls. The associations between *CYP2A13* and *CYP2A6* polymorphisms and risk of NPC were estimated by odd ratios (OR) and their 95% confidence intervals (CI), which were calculated by unconditional logistic regression. Light or heavy smokers were categorized by the 50th percentile pack-year value among controls, *i.e.*, <20 or ≥20 pack-years (cigarettes per day ÷ 20 × years smoked). The ORs were adjusted for age, gender, and smoking status. P values < 0.05 were considered as statistically significant. All analyses were performed using the Statistical Analysis System (Version. 6.12, SAS Institute, Cary, NC).

Results

In the present study, 437 NPC cases and 470 controls were recruited. All cases and controls were ethnic Cantonese. Characteristics of age, gender and smoking status of cases and controls are summarized in Table 1.

Allele frequencies and genotype distributions of *CYP2A13* and *CYP2A6* in cases and controls were shown in Table 2. Relatively low frequencies were observed for the minor alleles of both *CYP2A13* 3375*T*

and *CYP2A6 *4* alleles in this study, with the former being 0.08 and 0.09, and the latter being 0.08 and 0.10 in cases and controls, respectively. The results were similar to the reports from northern Chinese (Wang, 2003). The distribution of *CYP2A13* 3375*C/T* genotypes among controls (*CC*, 82.8%; *CT*, 17.2%; *TT*, 0%) was consistent with values predicted by the Hardy-Weinberg equilibrium ($P = 0.92$, Chi-square test). The frequencies of these three genotypes among NPC patients (*CC*, 84.9%; *CT*, 14.4%; *TT*, 0.7%) did not differ from the controls ($P = 0.11$, Chi-square test). The distribution of the *CYP2A6 *1/*1*, **1/*4*, and **4/*4* genotypes among controls was 80.7%, 18.7% and 0.6%, respectively and was also in accordance with the Hard-Weinberg equilibrium ($P = 0.87$, Chi-square test). The distribution of these *CYP2A6* genotypes among NPC patients (83.5%, 15.3%, and 1.2%) were not significant different from controls (80.7%, 18.7%, and 0.6%) ($P = 0.31$, Chi-square test). Unconditional logistic regression analysis was used to estimate associations between the genotypes and risk of NPC (Table 2). Since the *CYP2A13 TT* genotype and *CYP2A6 *4/*4* genotype were rare in this study in both cases (0.7% and 1.2%, respectively) and controls (0% and 0.6%, respectively), so the *TT* genotype was combined with *CT* genotype and **4/*4* genotype was combined with **1/*4* genotype for the subsequent estimation of risk for NPC. Neither the *CYP2A13* -3375*T* variants nor *CYP2A6 *4* variants were associated with increased risk of NPC (OR = 0.84, 95% CI = 0.59–1.20, and OR = 0.83, 95% CI = 0.58–1.18, respectively) compared with their wild genotypes. We next investigated whether there was a statistical interaction between the *CYP2A13* and *CYP2A6* genotypes associated with the risk of NPC. Combination analysis showed that individuals with both *CYP2A13 T* variants and *CYP2A6 *4* variants had no association with risk for NPC (OR = 0.71, 95% CI = 0.33–1.52) compared with those with both *CYP2A13 CC* and *CYP2A6 *1/*1* genotypes (Table 3).

Then we investigated whether an interaction existed between the examined genetic polymorphisms and smoking status. No association with the risk of NPC was observed in *CYP2A13 C/T* polymorphisms in smokers (OR = 0.75, 95% CI = 0.43–1.32), including after stratification of smoking status (Table 4). We did not observe the association between the *CYP2A6 *4* variant polymorphisms in smokers and risk of developing NPC (OR = 0.90, 95% CI = 0.27–1.70), even after stratification of smoking status (Table 5). Furthermore, we investigated the combination of two gene polymorphisms and smoking status. No association was observed between the two gene polymorphisms and smokers and risk of developing NPC, including the stratification of smoking status (Table 6).

Table 1. Characteristics of 437 cases and 470 control subjects

Variable	No. of Cases (%)	No. of Controls (%)	*P* value
Gender			
Male	234 (53.5)	232 (49.3)	0.11
Female	203 (46.5)	238 (50.7)	
Mean age (years)[a]	46.1 (12.1)	45.6 (15.7)	
Smoking status			
Non-smokers	157 (35.9)	321 (68.3)	< 0.001
Smokers[b]	280 (64.1)	149 (31.7)	
< 20 pack-years	97 (34.6)	65 (43.6)	< 0.001
≥ 20 pack-years	183 (65.4)	84 (56.4)	
Mean pack-years[a]	24.7 (15.6)	7.5 (14.7)	
Median pack-years	20	20	

[a] The values in parentheses are standard deviation; [b] Smokers included 4 ex-smokers.

Table 2. Genotypes and allele frequencies of *CYP2A13* and *CYP2A6* genotypes among cases and controls and their association with risk of nasopharyngeal carcinoma

Genotype	No. of Cases (%)	No. of Controls (%)	Adjusted OR[a] (95% CI)	*P* value
CYP2A13				
CC	371 (84.9)	389 (82.8)	1.00	
CT	63 (14.4)	81 (17.2)	0.80 (0.56-1.15)	0.23
TT	3 (0.7)	0 (0)		
CT+TT	66 (15.4)	81 (17.2)	0.84 (0.59-1.20)	0.34
T allele frequency	0.08	0.09		
CYP2A6				
**1/*1*	365 (83.5)	379 (80.7)	1.00	
**1/*4*	67 (15.3)	88 (18.7)	0.80 (0.55-1.14)	0.22
**4/*4*	5 (1.2)	3 (0.6)	1.76 (0.40-7.83)	0.45
**1/*4+*4/*4*	72 (16.5)	91(19.3)	0.83 (0.58-1.18)	0.31
**4* allele frequency	0.08	0.10		

[a] Odds ratios (OR) and 95% confidence intervals (CI) were calculated with the *CYP2A13* -3375*CC* or *CYP2A6* **1/*1* genotypes as the reference group and adjusted for age, sex and smoking status.

Table 3. Combined effect of *CYP2A13* and *CYP2A6* genotypes with risk of nasopharyngeal carcinoma

CYP2A13	*CYP2A6*	No. of Cases	No. of Controls	Adjusted OR[a] (95% CI)	*P* value
CC	**1/*1*	312	315	1.00	
CC	**1/*4+*4/*4*	59	74	0.82 (0.56-1.22)	0.33
CT+TT	**1/*1*	12	17	0.83 (0.55-1.25)	0.37
CT+TT	**1/*4+*4/*4*	13	17	0.71 (0.33-1.52)	0.38

[a] OR and 95% CI were calculated with the *CYP2A13* -3375*CC* and *CYP2A6* **1/*1* genotypes as the reference group and adjusted for age, sex and smoking status.

Table 4. Association between *CYP2A13* genotypes and risk of nasopharyngeal carcinoma stratified by smoking status

CYP2A13	Smoking status	No. of Cases	No. of Controls	Adjusted OR[a] (95% CI)	*P* value
CC	NO	128	265	1.00	
CT+TT	NO	29	56	0.95 (0.57-1.58)	0.85
CC	YES	243	124	1.00	
CT+TT	YES	37	25	0.75 (0.43-1.32)	0.32
CC	pack-years < 20	89	53	1.00	
CT+TT	pack-years < 20	8	12	0.42 (0.16-1.11)	0.08
CC	pack-years ≥ 20	154	71	1.00	
CT+TT	pack-years ≥ 20	29	13	1.01 (0.48-2.08)	0.99

[a] OR and 95% CI were calculated with the *CYP2A13* -3375*CC* genotype as the reference and adjusted for age and sex.

Table 5. Association between *CYP2A6* genotypes and risk of nasopharyngeal carcinoma stratified by smoking status

CYP2A6	Smoking status	No. of Cases	No. of Controls	Adjusted OR[a] (95%CI)	*P* value
**1/*1*	NO	129	258	1.00	
**1/*4+*4/*4*	NO	28	64	0.83 (0.49-1.38)	0.46
**1/*1*	YES	236	124	1.00	
**1/*4+*4/*4*	YES	44	27	0.90 (0.52-1.55)	0.70
**1/*1*	pack-years < 20	84	54	1.00	
**1/*4+*4/*4*	pack-years < 20	13	12	0.68 (0.27-1.70)	0.40
**1/*1*	pack-years ≥ 20	152	70	1.00	
**1/*4+*4/*4*	pack-years ≥ 20	31	15	0.97 (0.48-1.96)	0.94

[a] OR and 95% CI were calculated with the *CYP2A6 *1/*1* genotype as the reference and adjusted for age and sex.

Table 6. Association between *CYP2A13* and *CYP2A6* genotypes and risk of nasopharyngeal carcinoma stratified by smoking status

CYP2A13	*CYP2A6*	Smoking status	No. of Cases	No. of Controls	Adjusted OR[a] (95% CI)	*P* value
CC	**1/*1*	NO	106	212	1.00	
CC	**1/*4+*4/*4*	NO	22	53	0.80 (0.45-1.41)	0.43
CT+TT	**1/*1*	NO	23	45	0.92 (0.52-1.63)	0.77
CT+TT	**1/*4+*4/*4*	NO	6	11	0.87 (0.28-2.69)	0.81
CC	**1/*1*	YES	206	103	1.00	
CC	**1/*4+*4/*4*	YES	37	21	0.94 (0.51-1.73)	0.83
CT+TT	**1/*1*	YES	29	19	0.78 (0.41-1.48)	0.44
CT+TT	**1/*4+*4/*4*	YES	7	6	0.62 (0.20-1.91)	0.40
CC	**1/*1*	pack-years < 20	77	43	1.00	
CC	**1/*4+*4/*4*	pack-years < 20	12	10	0.68 (0.25-1.86)	0.45
CT+TT	**1/*1*	pack-years < 20	7	10	0.34 (0.11-1.04)	0.06
CT+TT	**1/*4+*4/*4*	pack-years < 20	1	2	0.20 (0.02-2.42)	0.21
CC	**1/*1*	pack-years ≥ 20	129	60	1.00	
CC	**1/*4+*4/*4*	pack-years ≥ 20	25	11	1.06 (0.47-2.35)	0.89
CT+TT	**1/*1*	pack-years ≥ 20	22	9	1.16 (0.50-2.71)	0.73
CT+TT	**1/*4+*4/*4*	pack-years ≥ 20	6	4	0.83 (0.22-3.07)	0.77

[a] OR and 95% CI were calculated with the *CYP2A13* -3375*CC* and *CYP2A6 *1/*1* genotype as the reference group and adjusted for age and sex.

Discussion

In this study, we examined whether genetic polymorphisms of *CYP2A13* and *CYP2A6*, alone and in combination, could have an impact on risk for developing NPC. Furthermore, we investigated the gene-environmental interactions with the risk of NPC. On the basis of 437 patients with NPC and 470 controls in a Cantonese population, we did not observe the polymorphisms of *CYP2A13* or *CYP2A6* influenced risk of developing NPC, including the combination of *CYP2A13* and *CYP2A6*. Furthermore, we did not observe association between risk of NPC and *CYP2A13* and *CYP2A6* variant genotypes, including when smoking was additionally stratified by pack-years smoked.

The expression of CYP2A13 in human tissue was

previsously reported predominantly in the respiratory tract (Su, 2000), and also observed in non-cancerous nasopharynx and NPC tissues (Jiang, 2004). CYP2A6 is mainly expressed in the liver, but is also found at low levels in other extra-hepatic organs including nasal tissue (Su, 1996). The expression of CYP2A13 and CYP2A6 in nasopharynx and the reported enzymatic activity relevant to carcinogens metabolism motivated us to investigate the relation between the genetic polymorphisms of *CYP2A13* and *CYP2A6* in NPC patients and evaluate possible association with environmental factors, such as smoking.

The single mutation of 3375C→T in *CYP2A13* was firstly identified by Zhang et al (2002), and then several groups reported the SNP in different tumors, including lung cancer (Wang, 2003; Cauffiez, 2004; Song, 2009). Wang et al (2003) found the variant allele of *CYP2A13* 3375*T* had a significantly reduced risk for the development of tobacco smoking-related lung cancer, furthermore, the protective effect of the SNP depends on smoking dose. Jiang et al (2004) reported no significant association between *CYP2A13* 3375*C/T* polymorphisms and risk of NPC in Cantonese. We performed another independent cohort in NPC patients and Cantonese controls, and furthermore, we included *CYP2A6* variants in this study, with additional smoking status. We did not observe the association between risk of NPC and *CYP2A13* variant genotypes, including when smoking was additionally stratified by pack-years smoked. This shows the function of CYP2A13 enzyme in developing NPC maybe different from lung cancer. The published studies regarding the association between the *CYP2A6* polymorphisms and lung cancer risk are conflict (Miyamoto, 1999; Tan, 2001). In addition, this defective *CYP2A6* allele showed no effect in a French population (Loriot, 2001). The group from Thailand (Tiwawech, 2006) investigated the relationship between NPC and *CYP2A6* polymorphisms in 74 NPC patients and 137 age-matched healthy controls, by distinguishing between a wild type allele, **1*, and two mutant alleles, **1B* and **4*. Overall, a significant association between *CYP2A6* polymorphism and NPC development was observed. Individual with mutant alleles had an increased risk for NPC when compared to those with **1/*1* genotype (OR = 2.37, 95% CI = 1.27–4.46). We enlarged the NPC patients and healthy controls to 437 and 470 and investigate the association between *CYP2A6 *4* variants and risk of NPC. But no association was observed between *CYP2A6 *4* variant and NPC risk when comparing with *CYP2A6 *1/*1* wild genotype, even after additional assessment with stratification by smoking status. The reason for inconsistent results between our study and Thailand's group maybe: 1, the samples from Thailand are small which may results in overestimate of the OR; 2, we focused on **4* variants genotypes of *CYP2A6* and Thailand's group investigated the combination of **1B* and **4* mutant alleles. We think our results maybe reflect the truly relationship between *CYP2A6 *4* polymorphism and risk of NPC.

The polymorphisms of *CYP2A13* and *CYP2A6* will result the reduced enzymatic activity in carcinogen, and results from lung cancer show the enzymes have important function in tumorigenesis of lung cancer (Wang, 2003; Miyamoto, 1999). We did not observe the relationship between polymorphisms of *CYP2A13* and risk of NPC, which was consistent with the results of Jiang et al (2004), neither the association of *CYP2A6 *4* variants and risk of NPC. Based on the results of this study, it shows that the effect of these two CYP2A13 and CYP2A6 enzymes are not so important in developing of NPC as in lung cancer.

In summary, no strong association was observed between the variant alleles of *CYP2A13* and *CYP2A6* and risk of developing NPC in the Cantonese population of southern China. Furthermore, we did not observe the interaction between genetic polymorphisms of *CYP2A13* and *CYP2A6* and smoking status in risk to develop NPC. The effect of these two enzymes maybe not so important in tumorigenesis of NPC as in lung cancer.

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