

Genetic polymorphisms in key DNA repair genes and risk of head and neck cancer in a Chinese population

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Abstract. Although tobacco and alcohol consumption are the major risk factors of head and neck cancer (HNC), genetic variations of genes involved in several biological pathways, such as DNA repair genes, may affect an individual's susceptibility to HNC. However, few studies have investigated the associations between polymorphisms in DNA repair genes and HNC risk in the Chinese population. Thus, we genotyped five common, non-synonymous single-nucleotide polymorphisms (SNPs) [*APEX1* (Asp148Glu), *XRCC1* (Arg399Gln), *ADPRT* (Val762Ala), *XPB* (Lys751Gln) and *XPG* (His1104Asp)] in a hospital-based, case-control study of 397 HNC cases and 900 cancer-free controls in China. The results showed that none of the five SNPs in the DNA repair pathway was significantly associated with HNC risk, suggesting that these polymorphisms may not play a major role in HNC susceptibility in this Chinese population.

Introduction

The incidence of head and neck cancer (HNC), especially squamous cell carcinoma of the head and neck (SCCHN), has markedly increased in the past 20 years and is now the fifth most common type of cancer worldwide (1). In the United States, it is estimated that there were 48,010 new cases and 11,260 deaths from SCCHN in 2010 (2). Accumulative evidence indicates that exposure to smoking and alcohol consumption are important risk factors of HNC (3); however, only few smokers and drinkers develop HNC, suggesting an individual susceptibility to this cancer in the general population. Most association studies on cancer susceptibility have focused on identifying effects of single-nucleotide polymorphisms (SNPs) in candidate genes of several pathways. Among

these, genes involved in the DNA repair pathway are the most investigated due to their vital role in protecting the genome from insults of environmental carcinogens (4,5). Studies have shown inter-individual variations of DNA repair capacity (DRC) in the general population and the effect of a suboptimal DRC on the risk of smoking-related cancers, such as lung cancer and SCCHN (6-8).

Of DNA repair pathways, nucleotide excision repair (NER) is the major repair mechanism for the DNA damage caused by tobacco smoking, which deals with a wide class of DNA damages, including bulky adducts cross-links, oxidative DNA damage, thymidine dimers and alkylating damage (9). NER involves more than 20 proteins whose inactivation may lead to xeroderma pigmentosum (XP) or Cockayne syndrome (CS). For example, rare mutations in xeroderma pigmentosum complementation group D and G (*XPB* and *XPG*) give rise to a combined XP/CS phenotype and are associated with severe neurological abnormalities.

The base excision repair (BER) pathway is another important mechanism that repairs DNA damage resulting from chemical alterations of a single base; a number of proteins are involved in repair steps, such as apurinic/apyrimidinic endonuclease (*APE1*, also known as *APEX1*), X-ray repair crosscomplementing 1 (*XRCC1*) and ADP-ribosyltransferase (*ADPRT*, also known as *PARP1*) (10). *APE1* is a key member in short-patch BER, which bridges the abasic sites of the damaged base by cleaving the DNA backbone at the 5' side to the abasic site and leaving a 3'-hydroxyl group and a 5'-deoxyribose phosphate group flanking the nucleotide gap (11). *ADPRT* plays a role in the long-patch BER by specifically binding to DNA strand breaks where it is autoactivated and recruits the *XRCC1*-*Lig3α* complex (12). Studies have shown that interactions of *ADPRT* with *XRCC1* as well as other partner proteins, such as *Polβ*, are critical for stimulating and executing BER processes (13).

Several functional genetic variants, particularly non-synonymous polymorphisms, have been identified in the *XPB*, *XPG*, *APE1*, *XRCC1* and *ADPRT* genes, and have shown a relationship with DRC variation and susceptibility to multiple cancers (14-26). Additionally, several reviews were also published to summarize the associations between functional variants of DNA repair genes and cancer risk, including HNC, and have provided meaningful results (17,20,26). However,

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most published studies on HNC risk and polymorphisms of DNA repair genes were conducted in a Caucasian population, but not in a Chinese population. Therefore, we hypothesize that common, non-synonymous single-nucleotide polymorphisms (nsSNPs) of the above genes may also contribute to the risk of HNC in China. To test this hypothesis, we conducted a case-control study of 397 patients with HNC and 900 cancer-free controls among a Chinese population.

Patients and methods

Study population. Our study was approved by the Institutional Review Board of Nanjing Medical University. All patients with histologically confirmed HNC were recruited from the Jiangsu Stomatological Hospital and the First Affiliated Hospital of Nanjing Medical University, China, from January 2009 to June 2011. Subjects with second HNC primary tumors or metastasized cancer from other organs were excluded from our study. Cancer-free controls were recruited from a cohort of >30,000 participants in a community-based screening program for non-infectious diseases in the Jiangsu Province, China and frequency-matched to the cases according to age (± 5 years) and gender. All subjects were genetically unrelated ethnic Han Chinese. All subjects were personally interviewed to collect demographic data (e.g., age and gender) and exposure information (e.g., smoking and drinking status). Each patient donated 5 ml of venous blood after providing a written informed consent. Of all subjects, 397 patients and 900 controls with adequate DNA samples were selected for TaqMan genotyping assay.

SNP selection and genotyping. According to the published literature and dbSNP database, we selected five common nsSNPs with minor allele frequency of >0.05 in Chinese Han in Beijing (CHB) [XPD Lys751Gln (rs13181), XPG His1104Asp (rs17655), APE1 Asp148Glu (rs1130409), XRCC1 Arg399Gln (rs25487) and ADPRT Val762Ala (rs1136410)] for genotyping, which have been most investigated for their associations with cancer risk in molecular epidemiological studies. Genomic DNA was extracted from the peripheral blood by the standard methods. Genotyping was carried out using the TaqMan allelic discrimination assay on an ABI 7900 system (Applied Biosystems, Foster City, CA, USA). Briefly, PCR primers and Taqman minor groove binder probes were designed and reactions were performed in 384-well microplates with ABI 9700 thermal cyclers (Applied Biosystems). The genotyping results were determined by System SDS software version 2.3. The accordance achieved 100% for the duplicates of 5% of the samples.

Statistical analysis. Differences in selected demographic variables, smoking status and drinking status between the cases and controls were evaluated using the Chi-square test. The associations between genotypes of selected polymorphisms and HNC risk were estimated by computing the odds ratios (ORs) and 95% confidence intervals (95% CIs) from both univariate and multivariate logistic regression analyses with adjustment for age, gender, smoking status and drinking status. Homogeneity tests were performed to evaluate the differences in stratum variable-related ORs. All statistical analyses were

Table I. Distribution of selected variables in HNC cases and cancer-free controls.

Variables	Cases		Controls		P-value ^a
	No.	%	No.	%	
All subjects	397	100	900	100	
Age (years)					
≤60 (median)	209	52.6	461	51.2	0.637
>60 (median)	188	47.4	439	48.8	
Gender					
Female	136	34.3	280	31.1	0.263
Male	261	65.7	620	68.9	
Smoking status ^b					
No	212	53.7	498	55.3	0.580
Yes	183	46.3	402	44.7	
Drinking status ^b					
No	217	54.9	609	67.7	<0.001
Yes	178	45.1	291	32.3	
Tumor site					
Oral cavity	293	73.8			
Oropharynx	6	1.5			
Larynx	88	22.2			
Other ^c	10	2.5			
Histology					
Squamous	335	84.4			
Other ^d	62	15.6			

^aTwo-sided Chi-square test. ^bSmoking and drinking information was not available for two subjects. ^cIncluding nasal sinuses, parotid and salivary gland. ^dIncluding adenocarcinoma, undifferentiated carcinoma and undetermined cancer.

performed with Statistical Analysis System software (version 9.1.3; SAS Institute Inc., Cary, NC, USA). The significance was established at $P < 0.05$ with a two-side test.

Results

As shown in Table I, there were no significant differences in the distributions of age and gender between the cases and the controls ($P = 0.637$ and 0.263 , respectively), suggesting that the matching for age and gender was satisfactory. Additionally, the difference in smoking status was also non-significant ($P = 0.580$); however, the proportion of drinkers in the cases was significantly higher than that in the controls (45.1 vs. 32.3%, $P < 0.001$). Of the 397 cases, 293 (73.8%) suffered from tumors of the oral cavity, 6 (1.5%) had oropharynx tumors, 88 (22.2%) had larynx tumors and 10 (2.5%) had tumors at other sites. Furthermore, 335 cases (84.4%) presented with squamous cell carcinoma.

The position, minor allele frequency (MAF) and P-values for genotype distributions of the five SNPs in the HapMap database are presented in Table II. The observed genotype frequencies for these five SNPs were all in Hardy-Weinberg equilibrium in the controls (all $P > 0.05$). The single locus analyses revealed that none of the single SNPs were

Table II. Primary information of selected SNPs in DNA repair genes.

SNP	Gene	Location	Base change	MAF in CHB (HapMap)	MAF in our controls	P-value ^a
rs13181	<i>ERCC2/XPD</i>	chr19	T>G, Lys751Gln	0.101	0.079	0.817
rs17655	<i>ERCC5/XPG</i>	chr13	G>C, Asp1104His	0.444	0.490	0.939
rs1130409	<i>APEX1</i>	chr14	T>G, Asp148Glu	0.476	0.422	0.065
rs25487	<i>XRCC1</i>	chr19	G>A, Arg399Gln	0.253	0.266	0.532
rs1136410	<i>ADPRT</i>	chr1	T>C, Val762Ala	0.470	0.416	0.887

^aChi-square test for genotyping distributions. MAF, minor allele frequency; CHB, Chinese Han in Beijing.

Table III. Logistic regression analysis for associations between polymorphisms of DNA repair genes and HNC risk.

Locus	Genotype	Case		Control		Crude OR (95% CI)	Adjusted OR (95% CI) ^a	P-value ^a
		No.	%	No.	%			
<i>XPD</i> rs13181	TT	333	84.5	752	84.8	1.00	1.00	
	TG	57	14.5	129	14.5	1.00 (0.71-1.40)	0.94 (0.67-1.33)	0.745
	GG	4	1.0	6	0.7	1.51 (0.42-5.37)	1.53 (0.42-5.54)	0.516
	TG/GG	61	15.5	135	15.2	1.02 (0.73-1.42)	0.97 (0.69-1.35)	0.857
	Additive					1.04 (0.77-1.41)	1.00 (0.73-1.36)	0.988
<i>XPG</i> rs17655	GG	108	27.4	234	26.5	1.00	1.00	
	CG	191	48.5	433	49.0	0.99 (0.75-1.32)	0.98 (0.74-1.31)	0.901
	CC	95	24.1	217	24.6	0.99 (0.71-1.37)	0.99 (0.71-1.38)	0.957
	CG/CC	286	72.6	650	73.5	0.95 (0.73-1.25)	0.95 (0.72-1.24)	0.685
	Additive					0.97 (0.82-1.15)	0.97 (0.82-1.15)	0.761
<i>APE1</i> rs1130409	TT	148	37.6	304	34.2	1.00	1.00	
	TG	159	40.4	420	47.2	0.78 (0.59-1.02)	0.77 (0.59-1.02)	0.065
	GG	87	22.1	165	18.6	1.08 (0.78-1.50)	1.08 (0.78-1.51)	0.641
	TG/GG	246	62.4	585	65.8	0.86 (0.68-1.11)	0.86 (0.67-1.11)	0.239
	Additive					1.00 (0.85-1.18)	1.00 (0.85-1.18)	0.982
<i>XRCC1</i> rs25487	GG	221	56.7	481	54.3	1.00	1.00	
	GA	146	37.4	339	38.3	0.94 (0.73-1.20)	0.96 (0.74-1.23)	0.729
	AA	23	5.9	66	7.5	0.76 (0.46-1.25)	0.81 (0.49-1.35)	0.421
	GA/AA	169	43.3	405	45.7	0.91 (0.71-1.15)	0.93 (0.73-1.19)	0.578
	Additive					0.90 (0.74-1.10)	0.93 (0.76-1.13)	0.453
<i>ADPRT</i> rs1136410	TT	138	34.9	300	34.0	1.00	1.00	
	TC	193	48.9	431	48.8	0.97 (0.75-1.27)	0.98 (0.75-1.28)	0.903
	CC	64	16.2	152	17.2	0.92 (0.64-1.31)	0.89 (0.62-1.28)	0.546
	TC/CC	257	65.1	583	66.0	0.96 (0.75-1.23)	0.96 (0.75-1.24)	0.752
	Additive					0.96 (0.81-1.14)	0.95 (0.80-1.13)	0.585

significantly associated with HNSCC risk. The genotype distributions of all SNPs in the cases and controls are shown in Table III. Similarly, the multivariate logistic regression analyses also showed that there were no significant associations between these five SNPs and HNSCC risk in different genetic models. For example, the adjusted ORs and 95% CI in the additive model were 1.00 (0.73-1.36) for rs13181, 0.97 (0.82-1.15) for rs17655, 1.00 (0.85-1.18) for rs1130409, 0.93 (0.76-1.13) for rs25487 and 0.95 (0.80-1.13) for rs1136410, respectively.

We further conducted the stratification analyses by age, gender, smoking, drinking, tumor sites and histology, but no significant associations were observed between the genotypes of the five SNPs and HNC risk in every stratum (data not shown). We also analyzed the two-way locus-locus and gene-environment interactions between all five SNPs and environmental factors (i.e., smoking status and alcohol status) using logistic regression models. Only one locus-locus interaction (rs1130409 and rs25487) was statistically significant (adjusted P_{int} 0.036), but changed to non-significant after the multiple test adjustment.

Discussion

In this case-control study, we assessed the associations of HNC risk with five nsSNPs in key DNA repair genes, which have been most widely studied in a variety of human cancers in other populations. The results showed that none of the five SNPs [*XPD* Lys751Gln (rs13181), *XPG* His1104Asp (rs17655), *APE1* Asp148Glu (rs1130409), *XRCC1* Arg399Gln (rs25487) and *ADPRT* Val762Ala (rs1136410)] were significantly associated with the risk of HNC in China.

XPD and *XPG* are two of more than 20 genes involved in NER. *XPD* codes an evolutionarily conserved helicase, a subunit of TFIIH that is essential for transcription and NER. The Lys751Gln (rs13181) polymorphism is located in exon 23 of *XPD* and causes codon 751 Lys (K) to be substituted for Gln (Q) (27). The *XPD* 751Gln allele was reported to be associated with higher DNA adduct levels in non-smokers (28) and phenotypes of repair of BPDE- and UV-induced DNA damage (14).

There have been several studies showing associations between this SNP and risk of multiple cancers, including HNC, but the results from different populations were confusing rather than conclusive (29-39). Recently, a meta-analysis with a total of 12 studies claimed that the *XPD* Lys751Gln polymorphism was not associated with HNC risk (17); however, no genotyping data from the Chinese population was included, with the exception of a Taiwan study with a small sample size of 154 cases and 105 controls (30). Our findings were consistent with those from the meta-analysis, suggesting that the *XPD* Lys751Gln polymorphism may not play a role in the susceptibility to HNC.

XPG mainly works as a structure-specific endonuclease that cleaves the damaged DNA strand on the 3' endside (40,41) and stimulates BER of oxidative DNA damage (42,43). The His1104Asp polymorphism (rs17655), located in exon 15 of *XPG*, has been largely investigated in studies on susceptibility to cancers of the breast (44), lung (45), stomach (46), bladder (47), colorectum (48) and head and neck (18,36,49,50). Although it was reported that the His1104Asp polymorphism of *XPG* together with SNPs of several other NER genes jointly contributed to the variability of DRC (16), we found that the His1104Asp polymorphism was not associated with the risk of HNC in China, supporting the results from other published studies for this SNP and HNC risk (18,36,49,50).

APE1, *XRCC1* and *ADPRT* are three crucial genes in the BER pathway and genetic variation in these genes may alter BER functions (51,52). In addition to DNA repair activity, *APE1* also regulates the gene expression as a redox co-activator of different transcription factors (11). The Asp148Glu polymorphism (rs3136820) is a T to G transversion at codon 148 of exon 5 in *APE1* and it has been reported to be related to hypersensitivity to ionizing radiation (53). Several studies have investigated the associations between Asp148Glu and cancer risk, but only two from Caucasians focused on HNC risk and neither found significant results (25,54).

Our study also failed to find significant associations between the Asp148Glu polymorphism and HNC risk in China. *XRCC1* plays an important role in BER by interacting with a complex of DNA repair proteins, including poly (ADP-ribose) polymerase, DNA ligase 3 and DNA polymerase β (55). The

Arg399Gln polymorphism (rs25487) is located at the region of the BRCT-I interaction domain of *XRCC1* and is linked with the reduced DRC (56,57). This polymorphism has been extensively investigated for its associations with cancer risk and the results were conflicting in different types of cancer or different populations (58-61); however, a meta-analysis including 7 studies indicated that Arg399Gln was not significantly associated with SCCHN risk in Caucasians and/or Asians (25), consistent with our findings in this study.

ADPRT is a DNA-dependent chromatin-associated enzyme, activated by DNA damage to catalyze polyADP-ribosylation of various proteins (62). The Val762Ala polymorphism (rs1136410) is located in exon 17 of *ADPRT*, leading to an amino acid exchange of valine to alanine. Although it has been suggested that the Val762Ala polymorphism contributes to altered *ADPRT* activity and carcinogenesis (63), only one study by Li *et al* has investigated the association of this SNP with SCCHN risk in the Caucasian population and found a protective effect of 762Ala allele on SCCHN risk (25). However, our current data provide evidence that this SNP does not have an effect on susceptibility to HNC risk in the Chinese population. Discrepancies in allele frequency may be a concern for the inconsistency between different studies. In the study by Li *et al*, the Gln allele frequency was 0.160 in Caucasians, while in our group, the Gln allele frequency was 0.416 in our Chinese population.

Several limitations of our study need to be addressed. Firstly, our study was a hospital-based case-control study, and inherent selection bias may lead to spurious findings. Secondly, the sample size of our study was relatively small, which may reduce the statistical power to detect the low penetrance effect of single locus, especially for the stratification and interaction analysis. Thirdly, only five functional SNPs were included in our study, and thus we cannot analyze the association between other SNPs in the DNA repair pathway and HNC risk in China.

In conclusion, this study provided evidence that five SNPs in key DNA repair genes [*XPD* Lys751Gln (rs13181), *XPG* His1104Asp (rs17655), *APE1* Asp148Glu (rs1130409), *XRCC1* Arg399Gln (rs25487) and *ADPRT* Val762Ala (rs1136410)] were not associated with HNC risk in China. The findings need to be validated by larger studies.

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