Association of Interleukin-10 (*IL10*) Promoter Genotypes with Nasopharyngeal Carcinoma Risk in Taiwan

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Abstract. *Nasopharyngeal carcinoma (NPC) is a multifactorial type of cancer, and cytokines driving the immune response seem to be disturbed in patients with NPC. Interleukin-10 (IL10) is an immunosuppressive cytokine which may facilitate carcinogenesis by down-regulating interferon-gamma production and supporting tumor escape from the immune response. We propose that differential expression levels of IL10 among individuals due to polymorphisms within the promoter of IL-10 gene, may be associated with NPC susceptibility. Therefore, the current study aimed at investigating the association of IL10 promoter genotypes with NPC and examining the interaction among the IL10 genotype and individual smoking habit in NPC susceptibility in Taiwan. A total of 698 native Taiwanese consisting of 176 cases and 522 controls were enrolled in this hospital-based study, and three single-nucleotide polymorphism sites at promoter regions of IL10, A-1082G (rs1800896), T-819C (rs3021097), and A-592C (rs1800872) were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and their interaction with smoking habit for NPC risk were evaluated. There were significantly different distributions of genotypic (p=0.0004) and allelic (p=0.0222) frequencies of IL10 A-1082G among NPC and controls. Individuals who carried AG or GG genotypes for IL10 A-1082G had a 1.91- and 3.26-fold higher risk of developing NPC compared to those who carried the AA genotype (95% confidence interval=1.28-2.85 and 1.35-7.85), respectively. None of the other polymorphisms investigated appeared to affect NPC risk. In gene-lifestyle interaction analysis, we have provided the first evidence ever to show that there is an obvious joint effect of IL10 A-1082G genotype with individual smoking habit on NPC risk. The results support the concept that interleukins may play a role in NPC development and that IL10 A-1082G, which is closely related to its protein expression, maybe a useful biomarker for NPC progression.*

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Nasopharyngeal carcinoma (NPC) is a cancer originating in the nasopharynx, the uppermost region of the pharynx, behind the nose where the nasal passages and auditory tubes join the remainder of the upper respiratory tract. It is a rare cancer in most countries around the world, with an incidence rate generally less than 1 per 100,000 persons/year. However, NPC incidence is extremely high in Southern China (25-30 per 100,000 persons/year) (1-3). In Taiwan, an intermediate-risk area, the annual incidence rates for males and females in 2007 were 8.41 and 2.93 per 100,000 persons/year, respectively (4). Compared with Western countries, the incidence rate is significantly higher in Taiwan, an island with a very high genetic conservation. Thus, genetic studies for Taiwanese are very useful, especially for evaluation of NPC susceptibility. In addition to Epstein-Barr virus (EBV) infection (5, 6), certain dietary factors (7) and genetic differences, such as single-nucleotide polymorphisms (SNPs), may all contribute to carcinogenesis of NPC (8-10), lifestyle factors such as smoking, may also play a role in the etiology of NPC (11-13).

Interleukin-10 (*IL10*) is a cytokine mainly produced by macrophages, T-helper-2 cells and B lymphocytes, which can both stimulate and suppress the immune responses, such as cytokine production, antigen presentation, macrophage activation and antigen-specific T-cell proliferation (14). In recent years, *IL10* has been reported to play a critical role in cancer development and metastasis (15, 16). Increased circulating *IL10* has been reported in patients with different

Table I. *The demographic and clinical characteristics of patients with nasopharyngeal carcinoma and controls.*

Characteristic	Controls (n=522)			Patients (n=176)			*p*-Value[a]
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			48.9 (9.8)			48.2 (11.1)	0.7104
Gender							1.0000
Male	379	72.6%		128	72.7%		
Female	143	27.4%		48	27.3%		
Indulgence							
Cigarette smoking	209	40.0%		77	43.8%		0.4252
Betel quid chewing	155	29.7%		55	31.3%		0.7046
Alcohol drinking	203	38.9%		80	45.5%		0.1319

[a]Based on Chi-square test.

types of cancer, including NPC (17-19). Clinically, overexpression of *IL10* is a useful prognostic factor in patients with NPC and may contribute to selecting patients with NPC who are candidates for aggressive therapy (20).

The *IL10* gene located on human chromosome 1q31-32 is composed of five exons and four introns. Three promoter SNPs, -1082 A/G (rs1800896), -819 T/C (rs3021097) and -592 A/C (rs1800872), have been reported to regulate the transcription of *IL10* messenger RNA and the expression of IL10 *in vitro* (21, 22). Recently, these polymorphisms of *IL10* have been examined for their contribution to some types of cancer, for instance, hepatocellular carcinoma (23), breast cancer (24) and renal cell carcinoma (25). In 2007, Wei and colleagues found that there were significant differences in the genotypic and allelic distribution of A-1082G polymorphism of the *IL10* gene between a population with NPC and healthy controls in mainland China. The -1082 AG and GG genotypes were associated with a significantly increased risk of NPC as compared with the -1082 AA genotype. Their results have also shown that the specific haplotype of *IL10* was associated with higher NPC risk (26). However, their sample size was relatively small (cases:controls=198:210), and the interaction of genetic and other factors was not examined. As far as we are aware, studies to date, have examined the association between genetic polymorphisms in *IL10* genes and NPC in a Chinese population. In this study, we aimed at examining whether *IL10* gene promoter A-1082G, T-819C and A-592C polymorphisms are associated with NPC in Taiwan. In addition, we also aimed to investigate the joint interaction of genotype with smoking behaviors.

Materials and Methods

Study population and sample collection. One hundred and seventy-six patients diagnosed with NPC were recruited at the outpatient clinics of general surgery between 2003-2009 at the China Medical University Hospital, Taichung, Taiwan. The clinical characteristics of patients including histological details were all graded and defined by expert surgeons. All patients voluntarily participated, completed a self-administered questionnaire and provided peripheral blood samples. As many healthy volunteers as controls were selected by matching for age, gender and habits after initial random sampling from the Health Examination Cohort of the hospital. The exclusion criteria of the control group included previous malignancy, metastasized cancer from other or unknown origin, and any familial or genetic diseases. Both groups completed a short questionnaire which included personal habits. Smokers were defined as daily or almost daily smokers who had smoked at least five packs of cigarettes in their lifetime. Age of smoking initiation, whether they were currently smoking or had already quit, and if so, when they had quit, and on average, how many cigarettes they smoked or had smoked daily were recorded for smokers.

Genotyping conditions. Each participant donated 3-5 ml venous blood and their genomic DNA was prepared within two days from their peripheral blood leucocytes with the protocol of a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and further processed and stored according to our regular methodology (9, 10, 27, 28). The primers used for *IL10* A-1082G were: forward 5'-CTC GCT GCA ACC CAA CTG GC-3', and reverse 5'-TCT TAC CTA TCC CTA CTT CC-3'; for T-819C were: forward 5'-TCA TTC TAT GTG CTG GAG AT-3', and reverse 5'-TGG GGG AAG TGG GTA AGA GT-3'; for A-592C were: forward 5'-GGT GAG CAC TAC CTG ACT AG-3', and reverse 5'-CCT AGG TCA CAG TGA CGT GG-3'. The following cycling conditions were used: one cycle at 94˚C for 5 min; 35 cycles of 94˚C for 30 s, 55˚C for 30 s, and 72˚C for 30 s; and a final extension at 72˚C for 10 min.

The PCR products were digested by *Mnl*I, *Mae*III, and *Rsa*I restriction enzymes for *IL10* A-1082G (cut from 139 bp A genotype into 106+33 bp T genotype), T-819C (cut from 209 bp T genotype into 125+84 bp C genotype) and A-592C (cut from 412 bp C genotype into 236+176 bp A genotype), respectively. Amplified and digested DNA products were monitored by electrophoresis on 3% agarose gels, stained with ethidium bromide and imaged under UV light.

Statistical analyses. Pearson's Chi-square test or Fisher's exact test (when the expected number in any cell was less than five) was used to compare the distribution of the *IL10* genotypic and allelic frequencies between case and control groups. The odds ratios (OR) together with 95% confidence intervals (CI) were calculated to

Table II. *Distribution of interleukin-10 (IL10) A-1082G (rs1800896) genotypic and allelic frequencies among patients with nasopharyngeal carcinoma and controls.*

A-1082G (rs1800896)	Controls		Patients		OR (95% CI)	*p*-Value[a]
	n	%	n	%		
Genotypic frequency						
AA	419	80.3%	117	66.5%	1.00 (Reference)	0.0004*
AG	92	17.6%	49	27.8%	1.91 (1.28-2.85)*	
GG	11	2.1%	10	5.7%	3.26 (1.35-7.85)*	
Carrier comparison						
AA+AG	511	97.9%	166	94.3%	1.00 (Reference)	0.0222*
GG	11	2.1%	10	5.7%	2.80 (1.17-6.71)*	
AA	419	80.3%	117	66.5%	1.00 (Reference)	0.0003*
AG+GG	103	19.7%	59	33.5%	2.05 (1.40-3.00)*	
Allelic frequency						
Allele A	930	89.1%	283	80.4%	1.00 (Reference)	2.99×10^{-5}*
Allele G	114	10.9%	69	19.6%	1.99 (1.43-2.76)*	

OR: Odds ratio, CI: confidence interval; [a]based on Chi-square test; *statistically significant.

Table III. *Distribution of interleukin-10 (IL10), T-819C (rs3021097) genotypic and allelic frequencies among patients with nasopharyngeal carcinoma and controls.*

T-819C (rs3021097)	Controls		Patients		OR (95% CI)	*p*-Value[a]
	n	%	n	%		
Genotypic frequency						
TT	285	54.6%	88	50.0%	1.00 (Reference)	0.5703
TC	185	35.4%	69	39.2%	1.21 (0.84-1.74)	
CC	52	10.0%	19	10.8%	1.18 (0.66-2.11)	
Carrier comparison						
TT+TC	470	90.0%	157	89.2%	1.00 (Reference)	0.7735
CC	52	10.0%	19	10.8%	1.09 (0.63-1.91)	
TT	285	54.6%	88	50.0%	1.00 (Reference)	0.2958
TC+CC	237	45.4%	88	50.0%	1.20 (0.85-1.69)	
Allelic frequency						
Allele T	755	72.3%	245	69.6%	1.00 (Reference)	0.3388
Allele C	289	27.7%	107	30.4%	1.14 (0.88-1.49)	

OR: Odds ratio, CI: confidence interval; [a]based on Chi-square test.

assess the relative risk conferred by a particular allele and genotype. Demographic and clinical data between groups were compared by Chi-square test and by Student's *t*-test. Data was assumed as significant at a statistical level when the *p*-value was less than 0.05.

Results

The demographic and clinical characteristics of patients with NPC and the non-cancer controls are summarized in Table I. There were no significant differences between the groups in their age, gender, cigarette smoking, betel quid chewing and alcohol drinking status (Table I). The analysis for the distribution frequencies of the genotypes and alleles of *IL10* A-1082G in the NPC and control groups are summarized in Table II. Firstly, there was a significant difference between NPC and control groups in the distribution of genotypic frequency (p=0.0004), and the ORs for AG and GG were 1.91 (95% CI=1.28-2.85) and 3.26 (95% CI=1.35-7.85) compared to that for the AA wild-type genotype. Secondly, we performed dominant and recessive comparisons, finding that the ORs of the AA+AG *versus* GG and AA *versus* AG+GG were 2.80 (95% CI=1.17-6.71, p=0.0222) and 2.05 (95% CI=1.40-3.99, p=0.0003), respectively. Lastly, for *IL10* A-1082G allelic frequency analysis, people carrying the G allele appear to have a 1.99-fold increased risk of NPC than those carrying the A allele (95% CI=1.43-2.76, $p=2.99\times10^{-5}$) (Table II). For the *IL10* T-819C (Table III) of A-592C (Table

Table IV. *Distribution of interleukin-10 (IL10), A-592C (rs1800872) genotypic and allelic frequencies among patients with nasopharyngeal carcinoma and controls.*

A-592C (rs1800872)	Controls		Patients		OR (95% CI)	*p*-Value[a]
	n	%	n	%		
Genotypic frequency						
AA	261	50.0%	93	52.8%	1.00 (Reference)	0.7947
AC	205	39.3%	66	37.5%	0.90 (0.63-1.30)	
CC	56	10.7%	17	9.7%	0.85 (0.47-1.54)	
Carrier comparison						
AA+AC	466	89.3%	159	90.3%	1.00 (Reference)	0.7765
CC	56	10.7%	17	9.7%	0.89 (0.50-1.58)	
AA	261	50.0%	93	52.8%	1.00 (Reference)	0.5422
AC+CC	261	50.0%	83	47.2%	0.89 (0.63-1.26)	
Allelic frequency						
Allele A	727	69.6%	252	71.6%	1.00 (Reference)	0.4883
Allele C	317	30.4%	100	28.4%	0.91 (0.70-1.19)	

OR: Odds ratio, CI: confidence interval; [a]based on Chi-square test.

IV), there was no difference in the distribution of either genotypic or allelic frequencies between patient and control groups. The conclusive finding deduced from the data in Tables II, III and IV is that the G allele of *IL10* A-1082G may serve as a risk biomarker for NPC in Taiwanese.

After finding that G-bearing genotypes of *IL10* A-1082G were associated with NPC risk, we investigated the interaction between the genotype of *IL10* A-1082G and cigarette smoking, betel quid chewing, and alcohol drinking habits. The genotypic distribution of AA, AG and GG of *IL10* A-1082G was significantly different between NPC and control smokers ($p=7.34\times10^{-5}$) (Table V). Consistent with the findings in Table II, the frequency of AG and GG genotypes were still significantly higher (29.9 and 10.4%) in patients with NPC with smoking habit than smoking controls (17.7% and 1.4%). There was no such distribution difference in the non-smoking groups ($p=0.1636$). There was found no obvious interaction between the genotype of *IL10* A-1082G and betel quid chewing or with alcohol drinking habits (data not shown).

Table V. *Distribution of interleukin-10 (IL10) A-1082G (rs1800896) genotypes in patients with nasopharyngeal carcinoma after stratification by cigarette smoking habit.*

Variable	*IL10* A-1082G (rs1800896) genotype			
	AA (%)	AG (%)	GG (%)	*p*-Value[a]
Smokers				
Controls	169 (80.9%)	37 (17.7%)	3 (1.4%)	7.34×10^{-5}*
Patients	46 (59.7%)	23 (29.9%)	8 (10.4%)	
Non-smokers				
Controls	250 (79.9%)	55 (17.6%)	8 (2.5%)	0.1636
Patients	71 (71.7%)	26 (26.3%)	2 (2.0%)	

[a]Based on Chi-square test; *statistically significant.

Discussion

Knowing that the expression levels of *IL10* may contribute to the carcinogenesis of NPC, we have selected three promoter polymorphic sites of the *IL10* gene, A-1082G (rs1800896), T-819C (rs3021097), and A-592C (rs1800872), and clarified their associations with susceptibility for NPC risk in a central Taiwan population. We found that the AG and GG genotypes of *IL10* A-1082G were significantly associated with a higher susceptibility for NPC in a Taiwanese population (Table II). This is supported by previous findings that the G allele of *IL10* A-1082G not only is associated with higher *IL10* expression, but with a higher frequency in undifferentiated carcinomas of nasopharyngeal type in Italian patients, as compared to healthy controls (29). In 2007, Wei and his colleagues also reported that the AG and GG genotypes of *IL10* A-1082G were associated with a significantly increased risk of NPC, as compared with the -1082 AA genotype, in a case–control study in a population in China with 198 patients with NPC and 210 healthy controls (26). However, in another investigation recruiting 160 patients with NPC and 156 healthy controls in Tunisia, the association between *IL10* genotype and NPC risk was not significant (30). For this inconsistency, we propose an explanation that the Han populations have genotypic backgrounds very similar to each other, but different from these of Western countries. One piece of evidence supporting this hypothesis could be provided by the basal genotypic frequencies of *IL10* A-1082G among the controls in these studies: AA, AG and GG percentages were

80.3, 17.6 and 2.1% for Taiwanese; 79.5, 18.1 and 2.4% for cases from mainland China; and 44.8, 38.5 and 16.7% for the Tunisian population, respectively. Noticeably, the latter population has an almost 8-fold higher frequency of the GG genotype. However, there is much higher risk of NPC for the two Eastern populations than the Western one. It is reasonable to suspect that a) the GG genotype of *IL10* A-1082G is a unique biomarker of NPC only for Eastern populations; b) the GG genotype of *IL10* A-1082G is a universal biomarker of NPC for both Eastern and Western populations, but the contribution of other SNPs and other factors such as a salty diet and polluted working place to NPC susceptibility should also be considered. All these possibilities should be further investigated in enlarged and broadened populations.

To investigate the joint effects of genotypic and lifestyle factors, we firstly analyzed the interactions of the *IL10* A-1082G genotype with factors such as smoking, betel quid chewing and alcohol drinking. The genotypes of *IL10* A-1082G indeed had joint effects with individual smoking habits on NPC susceptibility (Table V), while the risk AG or GG genotype for *IL10* may contribute very little to susceptibility in non-smokers (Table V). At the same time, no obvious joint effect of the *IL10* A-1082G genotype with either betel quid chewing or alcohol drinking habits on NPC was found.

Consistent with our results in NPC, the *IL10* A-1082G genotype seems to play an important role in lung (31, 32), cervical (33), breast (34), prostate (35), and gastric (36-38), melanoma (39) and gastroduodenal disease (40). Of course, there were several findings reporting no association of this SNP with various types of cancers (41-44). There is no denying that the sample sizes of all these studies need to be enlarged, and although their findings are valuable for comparison, any conclusion on the role that *IL10* genotype plays in carcinogenesis can not easily be made.

To sum up, to our knowledge, this is the first study which focuses on *IL10* and its synergistic effects with smoking habits on NPC risk in Taiwanese, where NPC prevalence is very high. The AG and GG genotypes of *IL10* A-1082G, together with the personal smoking habits, appear to play a critical role in the carcinogenesis of NPC.

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