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Association between interleukin-17 gene polymorphisms and the risk of laryngeal cancer in a Chinese population

F.Z. Si[1], Y.Q. Feng[2] and M. Han[3]

[1]Department of Otolaryngology,
The Second Affiliated Hospital of Xinjiang Medical University, Urumchi, China
[2]Department of Ophthalmology, Yanan University Affiliated Hospital, Yanan, China
[3]Department of ORL-HNS, Yanan University Affiliated Hospital, Yanan, China

Corresponding author: M. Han
E-mail: miaohan339@163.com

Genet. Mol. Res. 16 (1): gmr16019076
Received August 12, 2016
Accepted January 23, 2017
Published March 30, 2017
DOI http://dx.doi.org/10.4238/gmr16019076

ABSTRACT. *IL-17* is associated with the occurrence and development of laryngeal cancer. However, no study has reported the association between *IL-17* polymorphisms and laryngeal cancer susceptibility. Therefore, we analyzed the association of three polymorphism loci (rs2275913, 197 G/A; rs3748067, 383 A/G; and rs763780, 7488 T/C) of *IL-17A* and *IL-17F* with laryngeal cancer in the Chinese population. A case-control study was performed with 325 patients and 325 controls. Polymorphisms were detected by polymerase chain reaction and sequencing methods. SPSS17.0 software was used for statistical analysis. Allele and genotype frequencies of *IL-17A* rs2275913 were significantly different between patients and controls ($P < 0.05$). Frequencies of rs2275913 (197 G/A) AA and GA+AA genotypes compared to the GG genotype were significantly higher in patients than in controls, indicating the association of these genes with laryngeal cancer susceptibility; adjusted OR values were 2.54 (1.50-4.23) and 1.62 (1.19-2.17), respectively. Furthermore, individuals with the

GA+AA genotype, compared to the GG genotype, aged ≤60 years, with smoking and alcohol consumption habits, and without a family history of cancer showed a higher cancer risk (OR = 2.74, 95%CI = 1.41-5.23; OR = 2.11, 95%CI = 1.21-3.55; OR = 1.91, 95%CI = 1.02-3.70; OR = 1.99, 95%CI = 1.08-3.39, respectively). In conclusion, the rs2275913 *IL-17A* (197 G/A) is associated with the incidence and development of laryngeal cancer in the Chinese population, and the AA and GA+AA genotypes harbor a high laryngeal cancer risk.

Key words: IL-17; rs2275913; rs3748067; rs763780; Laryngeal cancer; Gene polymorphism

INTRODUCTION

Laryngeal cancer is one of the most common cancers of the head and neck parts of the human body, accounting for 1-5% of all malignancies (Rudolph et al., 2011; Bobdey et al., 2015; Luo et al., 2015). More than 90% of laryngeal cancers are of the squamous cell carcinoma type (Qadeer et al., 2006; Rutt et al., 2010). The incidence rate of the disease comes second only to that of nasopharyngeal cancer in South China (Zhang et al., 2015b). In the past 10 years, the incidence rate of laryngeal cancer has been rising steadily because of the role of different carcinogenic factors and exposure to environmental factors (Ramroth et al., 2008). Although tobacco smoking and alcohol consumption are considered to be the main risk factors of laryngeal cancer, only a small proportion of people contracted the disease when exposed to these factors, suggesting that genetic susceptibility may play an important role in the occurrence and development of this cancer type. Studies have shown that various genes are associated with the occurrence, development, metastasis, and prognosis of laryngeal cancer, such as *Ccbe1*, *EGFR*, *COX-2*, *Survivin*, *VEGF*, *IL-13*, *IL-17*, etc. (Homer et al., 2001; Yalcin et al., 2004; Li et al., 2009; Facucho-Oliveira et al., 2011; Lionello et al., 2014).

At present, it has been suggested that cytokines play an important role in immune regulation, and any imbalance in the immune system can lead to diseases, including cancer (Eichbaum et al., 2011; Schapher et al., 2011). Interleukin 17 (IL-17) was originally cloned from the cDNA sequence of a hybrid rodent T cell in 1993 and named CTLA-8 by Rouvier (Singh et al., 2016). In 2005, a new type of T helper cell named Th17 was discovered following the investigation of IL-17 (Punt et al., 2015). To date, six family members of IL-17A have been identified, namely IL-17A to IL-17F. IL-17 exhibits biological effects by combining with the IL-17 receptor (IL-17R). Studies have shown that *IL-17* single nucleotide polymorphisms (SNPs) are associated with many diseases (Wang et al., 2014; Jiang et al., 2015). However, to date, no study has referred to the correlation between *IL-17* polymorphisms and laryngeal cancer. Therefore, we recruited a population of Chinese Han individuals and used case control methods to investigate the relationship between *IL-17* polymorphisms and laryngeal cancer.

MATERIAL AND METHODS

Subjects

From November 2011 to July 2015, we recruited 325 patients (300 males and 25

females) with laryngeal cancer from the Second Affiliated Hospital of Xinjiang Medical University and Yanan University Affiliated Hospital. The average age of patients was 60.5 ± 8.2 years. The patient age ranged from 43 to 82 years. Patients were selected on the basis of the following inclusion criteria: 1) primary tumor diagnosed pathologically as squamous cell carcinoma; 2) no prior exposure to radiotherapy and chemotherapy; 3) intact blood samples; 4) complete clinical data records; 5) patients unrelated by blood; 6) smokers were preferred. Healthy individuals (N = 325), without laryngeal cancer or other obvious disease symptoms and age-matched to ± 5 years with the patient group, were selected as controls from the Chinese Han population. The control group was recruited from the Second Affiliated Hospital of Xinjiang Medical University and Yanan University Affiliated Hospital. This group did not include individuals related by blood or with a history of cancer. The ages of individuals in the control group ranged from 45 to 78 years, with an average age of 61.8 ± 5.7 years.

All study subjects provided written informed consent. The epidemiological survey conducted included data on demographics, alcohol consumption and tobacco smoking status, and family history of cancer. At the same time, blood samples (5 mL each) were collected and used for genomic DNA extraction. This study was approved by the ethics committee of the Second Affiliated Hospital of Xinjiang Medical University and Yanan University Affiliated Hospital.

DNA extraction and genotyping

Blood samples (5 mL each) were collected in vacuum sterile ethylenediaminetetraacetic acid tubes from the patient and control groups. Blood was centrifuged at 4°C and 1300 r/min for 10 min. Genomic DNA was extracted by the QIAamp DNA Blood Mini kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions.

Polymerase chain reaction (PCR) and DNA sequence analysis methods were used for DNA amplification and sequence analysis. The primers were designed by the Autoprimer tool (http://www.autoprimer.com) and synthesized by the Shanghai SangGong production company; primer sequences are listed in Table 1. The 50 µL PCR reaction system included the following: 75 µM dNTPs, 20 ng genomic DNA, 50 nM primers, 3.5 mM $MgCl_2$, and 0.5 U Hotstar Taq polymerase. A 96-well plate was used for the 40-cycle PCR reaction with the following reaction parameters: 95°C for 15 min, 94°C for 30 s, 55°C for 30 s, 72°C for 60 s, and 72°C for 7 min, followed by incubation of the mixture at 4°C. The PCR products were sequenced and analyzed by the DNASTAR Lasergene sequence analysis software (Madison, WI, USA) and compared by the MEGA5.0 software (Pennsylvania State University, PA, USA).

Table 1. PCR primers used in this study.

SNPs	Primers	Sequences (5'-3')
rs2275913	Forward	GCAGTTGTGCTCAGCTTCTAA
(197 G/A)	Reverse	TTCAGGGGTGACACCATTTT
rs3748067	Forward	CTGTTTCCATGGCTGCAGGTC
(383 A/G)	Reverse	TGGTGAGCTGGTTCTGCACTT
rs763780	Forward	CTGTTTCCATGGGTGCACCTC
(7488 T/C)	Reverse	TCCTGACTGTTCTCCGCACCT

Statistical analysis

The SPSS17.0 software was used for statistical analysis. General data of the case

and control groups were compared by the *t*-test or chi-square test. The genotype frequency of the control population was tested by the chi-square goodness-of-fit test to assess the Hardy-Weinberg equilibrium (HWE) and, therefore, determine if there was group representation. In the patient and control groups, differences in genotype, allele, and haplotype frequencies were tested by the chi-square test. Logistic regression analysis of single and multiple factors was used to calculate the OR and 95%CI values. The statistical significance of genotypes was analyzed by the stratification analysis method. $P < 0.05$ was considered statistically significant.

RESULTS

General data of the patient and control groups are shown in Table 2. The age distribution between patients with laryngeal cancer and the control group had no statistical significance ($P = 0.199$), while the proportion of smokers, alcohol consumers, and individuals with a family history of cancer was significantly higher in the patient group than in the control group ($P < 0.001$). Laryngeal cancer was confirmed in patients according to the tumor-node-metastasis classification (2002) system by the union for international cancer control. Out of the 325 patients included in this study, there were 6 cases of Stage 0, 81 cases of Stage I, 91 cases of Stage II, 120 cases of Stage III, and 27 cases of Stage IV cancer. Moreover, there were 156 cases of well differentiated carcinoma, 117 cases of moderately differentiated carcinoma, and 52 cases of poorly differentiated carcinoma in the patients.

Table 2. Comparison of general data between the patient and control groups.

Parameters	Patients	Controls	*t*-value or χ^2 value	P value
Age (years)	60.5 ± 8.2	61.8 ± 5.7	1.763	0.885
≤60	179 (55.1%)	156 (48.0%)	3.26	0.199
>60	146 (44.9%)	169 (52.0%)		
Sex				
Male	300 (92.3%)	300 (92.3%)		
Female	25 (7.7%)	25 (7.7%)	0.00	1.00
Smoking status				
Non-smokers	47 (14.5%)	166 (51.1%)	98.89	<0.001
Smokers	278 (85.5%)	159 (48.9%)		
Alcohol consumers				
No	99 (30.5%)	223 (68.6%)	94.63	<0.001
Yes	226 (69.5%)	102 (31.4%)		
Family history of cancer				
No	237 (72.9%)	300 (92.3%)	42.51	<0.001
Yes	88 (27.1%)	25 (7.7%)		
Tumor grading				
Well differentiated	156 (48.0%)			
Moderately differentiated	117 (36.0%)			
Poorly differentiated	52 (16.0%)			
Clinical stages				
Stage 0	6 (1.8%)			
Stage I	81 (24.9%)			
Stage II	91 (28.0%)			
Stage III	120 (36.9%)			
Stage IV	27 (8.4%)			
Clinical classification				
Trans form	20 (6.2%)			
Inferior type	3 (0.9%)			
Glottic	196 (60.3%)			
Supralottic	106 (32.6%)			

Distribution of rs2275913, rs3748067, and rs763780 loci in the control group were in accordance with the Hardy Weinberg equilibrium ($\chi^2 = 0.131$; 0.126; 0.142, and P =

0.717; 0.819; 0.636, respectively). The distribution and allele frequency of the three loci for susceptibility to laryngeal cancer in the patient and control groups are presented in Table 3. The allele and genotype frequencies of *IL-17A* rs3748067 and *IL-17F* rs763780 in patients with laryngeal cancer and the control group were not statistically significant (P > 0.05), while the allele and genotype frequencies of *IL-17A* rs2275913 between the patient and control groups were significantly different (P < 0.05). Multivariate logistic regression analysis, after adjusting for age, smoking status, alcohol consumption, and a family history of cancer, showed that the AA and GA+AA genotypes, compared to the GG genotype, increased laryngeal cancer risk significantly (adjusted OR = 2.54, 95%CI = 1.50-4.23; OR = 1.62, 95%CI = 1.19-2.17, respectively).

Table 3. Distribution and frequency of the three loci with susceptibility of laryngeal cancer.

Genotype of *IL-17*	Patients	%	Controls	%	[1]OR (95%CI)	P value
rs2275913						
GG	121	37.23	155	47.69	Ref.	
GA	148	45.54	146	44.92	1.03 (0.93-1.97)	0.71
AA	56	17.23	24	7.39	2.54 (1.50-4.23)	<0.001
GA+AA	204	62.77	170	52.31	1.62 (1.19-2.17)	0.002
rs3748067						
TT	273	84	285	87.69	Ref.	
TC	33	10.15	31	9.54	1.08 (0.66-1.96)	0.49
CC	19	5.85	9	2.77	1.36 (0.79-3.95)	0.12
TC+CC	52	16	40	12.31	1.31 (0.88-2.07)	0.16
rs763780						
CC	265	81.54	277	85.23	Ref.	
CT	35	10.77	36	11.08	1.12 (0.69-1.97)	0.44
TT	25	7.69	12	3.69	1.43 (0.80-3.21)	0.1
CT+TT	60	18.46	48	14.77	1.29 (0.81-2.01)	0.19

[1]Adjusted for gender, age, family history of cancer, smoking status, and alcohol consumption.

For further investigation, we performed a stratified analysis of the genotype distribution and susceptibility to laryngeal cancer. The association between distribution of the rs2275913 locus genotype and susceptibility to laryngeal cancer was stratified by age, smoking status, alcohol consumption, and a family history of cancer. Results of the analysis are shown in Table 4. An increased cancer risk was observed in patients bearing the GA+AA genotype, compared to the GG genotype, aged ≤60 years old (OR = 2.74, 95%CI = 1.41-5.23), with a habit of smoking (OR = 2.11, 95%CI = 1.21-3.55) and alcohol consumption (OR = 1.91, 95%CI = 1.02-3.70), and without a family history of cancer (OR = 1.99, 95%CI = 1.08-3.39).

Table 4. Stratified analysis of the rs2275913 genotypes with susceptibility to laryngeal cancer.

Groups	N		GG		AA		OR value	P value	GA+AA		OR value	P value
	Patients	Controls	Patients	Controls	Patients	Controls			Patients	Control		
Age												
≤60	179	156	57	79	26	12	1.02 (0.54-1.94)	>0.05	125	75	2.74 (1.41-5.23)	<0.05
>60	146	169	64	76	30	12	1.04 (0.44-2.46)	>0.05	79	95	1.33 (0.63-2.81)	>0.05
Smoking status												
Non-smokers	47	166	20	77	9	12	1.03 (0.43-2.44)	>0.05	26	90	1.81 (0.60-5.44)	>0.05
Smokers	278	159	101	78	47	12	0.98 (0.42-2.33)	>0.05	178	80	2.11 (1.21-3.55)	<0.05
Alcohol consumption												
No	99	223	35	102	16	16	1.02 (0.51-2.05)	>0.05	66	122	2.07 (0.96-4.49)	>0.05
Yes	226	102	86	53	40	8	0.96 (0.39-2.39)	>0.05	138	48	1.91 (1.02-3.70)	<0.05
Family history of cancer												
No	237	300	84	140	39	22	0.99 (0.49-1.97)	>0.05	155	162	1.99 (1.08-3.39)	<0.05
Yes	88	25	37	15	17	2	0.85 (0.18-3.97)	>0.05	49	8	1.68 (0.42-6.67)	>0.05

DISCUSSION

IL-17A and IL-17F are important pro-inflammatory cytokines that can be expressed in many cell types (Wedebye Schmidt et al., 2013; Giles et al., 2016; Orosz et al., 2016). They can induce the secretion of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), IL-1, IL-6, IL-18, granulocyte macrophage colony, colony growth stimulating factor, chemokines, antimicrobial peptides (mucin, β defense element, and S100A-9 protein), matrix metalloproteinase 1, and NF-κB receptor activation factor ligand expression, causing tissue invasion and damage (Chabaud et al., 2001; Kordasti et al., 2009; Qu et al., 2013). Several studies have focused on the relationship between inflammation and inflammation-related tumors (Seljelid and Busund, 1994; Trakatelli et al., 2005); however, the specific function of IL-17 in tumors has not been elucidated and study results have been inconsistent. IL-17 may induce chemotactic factor production and dendritic cell recruitment, resulting in anti-tumor cytotoxic effects (Schirmer et al., 2010; Carmona et al., 2012). On the contrary, IL-17 can induce the activation of IL-6 for the signal transducer and activator of transcription 3 (stat3) pathway and anti-apoptosis and promote vascular endothelial growth factor expression, playing an important role in tumor growth promotion (Gu et al., 2011).

Many studies have shown that *IL-17* or its receptor polymorphisms were associated with the occurrence and development of autoimmune diseases, such as asthma, and the severity of rheumatoid arthritis (Tabarkiewicz et al., 2015; Zhang et al., 2015a). Meanwhile, *IL-17* polymorphisms were associated with inflammatory bowel disease and the occurrence and development of gastric cancer (Wang et al., 2014; Bank et al., 2015; Qi et al., 2015; Zhao et al., 2016). However, there have been no studies on the relationship between *IL-17* polymorphisms and susceptibility to laryngeal cancer, lending significance to the present study.

Previously, laryngeal cancer was known to be closely related to environmental factors, although its incidence rate was not high, accounting for only 1-5% of all cancers (Saedi et al., 2009). However, with increasing environmental pollution and lifestyle changes, the incidence of laryngeal cancer has been increasing yearly. In 2008, approximately 150,000 new cases of laryngeal cancer were reported worldwide (Saedi et al., 2009). Smoking and alcohol consumption are one of the most prominent factors in the occurrence of this cancer type. Other causative factors include sulfur dioxide and car exhaust emissions; asbestos, mustard gas, and other occupational exposures; and heavy metals (Russo et al., 1996; Menvielle et al., 2004; Romanowicz-Makowska et al., 2012). In this study, 85.5% of laryngeal cancer patients and 48.9% of the control group were habitual smokers and 69.5% of laryngeal cancer patients and 31.4% of the control group were habitual alcohol consumers. These two indicators had significantly different values between the patient and control groups. Study results showed that the rs2275913 polymorphism of *IL-17A* in the laryngeal cancer group and the control group occurred with a statistically significant frequency, and a significantly higher risk of laryngeal cancer was observed to be harbored by the AA and GA+AA genotypes than the GG genotype. Additionally, we observed that there was an increase in laryngeal cancer risk because of the influence of smoking, alcohol consumption, and other factors in patients with the GA+AA genotype, suggesting that these factors are independent carcinogenic factors that interact with genes.

A major strength of this study is that the control and patient groups were age-matched. Moreover, the 1:1 matched case-control study design, which improves the effectiveness of statistical analysis, was not employed by other studies on this topic. However, the results of our study are subject to two limitations. First, the study participants were selected from only

one hospital; therefore, the sample population did not represent the overall population. However, the gene distributions of rs4938723 in the control group were in line with the HWE, suggesting that the samples could represent the general population. Second, the sample size was relatively small in our study, which may have reduced the statistical power of our analysis. Therefore, further studies with larger sample sizes are greatly needed to validate our study results.

At present, there is scarce research on the correlation between *IL-17* SNPs and diseases, especially laryngeal cancer. Our study aimed at investigating this correlation in the Chinese Han population; therefore, studies on other ethnic groups should be conducted. The study of *IL-17* SNPs could contribute to the understanding of diseases associated with them and targeted therapy.

CONCLUSION

IL-17A and IL-17F are important pro-inflammatory cytokines that can be expressed in many cell types. IL-17 can induce IL-6 activation for the stat3 pathway and anti-apoptosis and promote vascular endothelial growth factor expression, playing an important role in tumor growth promotion. The rs2275913 polymorphism of *IL-17A* (197 G/A) was found to be associated with the incidence and development of laryngeal cancer in the Chinese population, and the AA and GA+AA genotypes were found harbor a high risk for laryngeal cancer.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We thank the Second Affiliated Hospital of Xinjiang Medical University and Yanan University Affiliated Hospital personnel for their help in the recruitment of study participants.

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