Interaction of Interleukin-16 Genotypes With Betel Quid Chewing Behavior on Oral Cancer in Taiwan

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Abstract. Background/Aim: Interleukin-16 (IL-16) is reported to play an important role in inflammation, carcinogenesis and tumoricidal processes, however, the contribution of IL-16 genotype to oral carcinogenesis is still largely unrevealed. Thus, the study aimed to investigate the contribution of IL-16 genotypes to Taiwan oral cancer risk. Materials and Methods: The genotypes of IL-16 rs4778889, rs11556218, and rs4072111 were revealed among 958 oral cancer cases and 958 control subjects by polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP). Results: First, the distributions of genotypic (p = 0.0004) and allelic (p = 0.0001) frequencies of IL-16 rs11556218 were significantly different between the case and control groups. In detail, the frequencies of IL-16 rs11556218 TG and GG were 28.1 and 5.8%, respectively, among oral cancer patients, significantly higher compared to those among controls (25.0% and 2.7%, respectively). Second, no difference was observed regarding IL-16 rs4778889 or IL-16 rs4072111. Last, there was a synergistic effect of betel quid chewing behavior and risky IL-16 rs11556218 genotype on oral cancer risk. Conclusion: The study indicates that the IL-16 rs11556218 G allele synergistically interacts with betel quid chewing behavior, contributing to increased risk of oral cancer in Taiwanese.

From the viewpoint of epidemiology, oral cancer is the tenth most commonly diagnosed cancer worldwide, with the highest incidence density in Taiwan (1). According to the updated annual report from the Taiwan government, oral cancer is the fourth cause of cancer-related deaths among males in Taiwan and the fifth among all Taiwanese (2). For many years, betel quid chewing habit has been identified as the most effective environmental contributor to oral cancer risk for Taiwanese (3). Although the surgery, therapy and medical caring services for oral cancer have made rapid progress during the past decade, the prevalence and death rate of oral cancer are still very high in Taiwan. Thus, early detection and prediction biomarkers for oral cancer risk are in urgent need.

Interleukin-16 (IL-16) is encoded by the IL-16 gene located on chromosome 15q26.3, composed of 631 amino acids and cleaved by caspase 3 to the active IL-16 protein, comprising the 121 amino acid C-terminal (4-6). IL-16 is in charge of activating several types of cells, including CD4+ T cells, monocytes, macrophages, eosinophils, and dendritic cells, and promotes the secretion of inflammatory cytokines, such as IL-1β (7), TNF-α, and IL-15 (8). Interestingly, a
significant increase in the IL-16 expression level has been widely reported in a panel of cancer tissues (9-15). In 2008, a genome-wide association study reported that IL-16 polymorphic differences in people may serve as a practical marker for prostate cancer prediction (16). In the next year, Thomas and his colleagues reported that the frequency of the G allele in IL-16 rs11556218 polymorphism can serve as a risk predictor for colorectal and gastric cancer (15), with no gender prevalence in any of them. At the same time, it was shown that women more frequently carrying the T allele in IL-16 rs4072111 had a lower risk of colorectal and gastric cancer compared to those carrying the C allele more (15).

Despite the significant involvement of IL-16 in cancer etiology and pathogenesis, no investigation about the contribution of IL-16 genotypes or phenotypes to oral cancer risk has been performed. Based on what has been published, we are interested to assess whether rs4778889 T/C, rs11556218 T/G and rs4072111 C/T polymorphisms of IL-16 are associated with a higher risk of oral cancer in Taiwan. In addition, we examined the joint effect of betel quid chewing status and particular IL-16 polymorphisms on oral cancer risk.

Materials and Methods

**Investigated controls and cases.** Briefly, 958 oral cancer cases were recruited at the China Medical University Hospital in central Taiwan (17-19). The demographic indexes of the oral cancer patients, including their histological details, were all graded and defined by expert surgeons. Each of the cancer patients voluntarily provided 5 ml of their peripheral blood and completed a questionnaire that focused on medical history and habits, such as diet, alcohol consumption, areca chewing and smoking. Then, the same number of healthy individuals with no cancer were selected to form the control group matched by age and gender after an initial random sampling from the Health Examination Cohort pool. They too contributed blood and completed the same questionnaire as the cancer patients. Self-reported habits, such as alcohol consumption, areca chewing and smoking were evaluated and classified as categorical variables. The personal frequencies of these personal behaviors, including alcohol consumption, areca chewing and smoking, as more than twice a week for years was recorded as a status/habit. These factors were recorded and are concisely summarized in Table I. The male versus female ratio was 76% to 24% in both control and oral cancer patient groups, perfectly matched with one another. The prognosis status of all the oral cancer patients, such as recurrence, metastasis and survival, were followed at least twice per year after their surgery. The mean age of the patients and the controls was 56.4 (SD=7.5) and 56.8 (SD=8.7) years, showing that the matching was successful, causing a non-significantly differential distribution between the case and control groups. The study was reviewed and approved by the Institutional Review Board (DMR101-IRB1-306).

**Oral cancer IL-16 genotyping methodology.** Genomic DNA from the peripheral blood leucocytes of all oral cancer patients and matched controls were extracted using the QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and further processed in typical polymerase chain reaction (PCR) processes as in our previous papers (20-22). The sequences of designed forward and reverse primers, corresponding restriction enzymes (New England BioLabs, Ipswich, MA, USA) and sizes of PCR products after enzyme digestion for oral cancer IL-16 genotyping identification are shown in Table II. The PCR cycling were set as: i) one cycle at 94°C for 5 min, ii) 35 cycles of 94°C for 30 s, iii) 55°C for 30 s, iv) 72°C for 30 s, and v) a final extension at 72°C for 10 min. The PCR products were run on a 3% agarose gel on 100 Volt for 20 min. The genotyping procedure was performed by three researchers independently and blindly. The repeated results from different researchers within each subject were perfectly consistent.

**Statistical analyses.** First, the Student’s t-test was used to compare the distribution of ages between the two groups. Second, Pearson’s chi-square test was applied to compare the distribution of the IL-16 rs4778889, rs11556218 and rs4072111 genotypes among the subgroups, and to also examine the possible interaction among the indices of interest. Last, the association between the IL-16 rs4778889, rs11556218 or rs4072111 polymorphisms and oral cancer risk were estimated using computing odds ratios (ORs) and their 95% confidence intervals (CIs) using logistic regression analysis. Any difference with the outcome of p<0.05 was considered statistically significant.

**Results**

Table I summarizes the demographic characteristics of the 1,916 recruited subjects (958 oral cancer cases and 958 non-cancer healthy controls) of this study. There is no significant difference with respect to age and gender, while smoking, alcohol consumption and betel quid chewing all have
different distribution between the oral cancer and control cohorts. These differences suggest that smoking, alcohol drinking and betel quid chewing are all risk factors for oral cancer in Taiwan (Table I). With regard to pathological identification, the major tumor sites of oral cancer occurred in the tongue (41.4%) and buccal mucosa (37.2%) (Table I).

In Table III, we have calculated the distributions of genotypic frequencies of the three \textit{IL-16} SNPs (rs4778889, rs11556218 and rs4072111) for all the 1916 investigated subjects. First, the allelic frequencies in the rs4778889, rs11556218 and rs4072111 of the control group agreed well with the Hardy-Weinberg equilibrium (all \(p>0.05\)). Second, in \textit{IL-16} rs4778889, there was no significant difference between the case and control groups concerning the frequency of TT, CT and CC (Table III, top panel, \(p\) for trend\(>0.05\)). Third, there was a noticeably significant difference in the distribution of \textit{IL-16} rs11556218 genotypic frequencies with regards to the TT, TG and GG genotypes between the case and control groups (Table III, middle panel, \(p\) for trend\(=0.0004\)). Furthermore, we found that TG, GG and TG+GG genotypes were differentially distributed between the case and control groups, compared to that of the wild-type TT genotype (Table III, middle panel, all \(p<0.05\) and OR>1.00). Last, concerning \textit{IL-16} rs4072111, there was no significant difference between the case and control groups with regards to the frequency of the CC, CT and TT genotypes (Table III, bottom panel, \(p\) for trend\(>0.05\)). Overall, it seems that only the \textit{IL-16} rs11556218 polymorphism, and not \textit{IL-16} rs4778889 or rs4072111, can serve as a predictive biomarker for higher risk of oral cancer in Taiwan.

| Polymorphic site | 5' to 3' primer sequences | Restriction enzymes | Allelic type and product size after digestion (bp) |
|------------------|----------------------------|---------------------|---------------------------------------------------|
| rs4778889        | CTCCACACTCAAAGCCCTTT       | \textit{HpaI}       | T: 280                                            |
|                  | CCATGTAAAACGGTGAGCTC       |                     | C: 246+34                                         |
| rs11556218       | GCTCAGGTTCCAGATGTGTT       | \textit{NdeI}       | G: 171                                            |
|                  | TGTGACAATCACAGCTTGGC       |                     | T: 147+24                                         |
| rs4072111        | CACTGTGATCCGGTCCAGT        | \textit{BsmA I}     | C: 164                                            |
|                  | TTAGGTACAAAACCCAGCCA       |                     | T: 140+24                                         |

Table III. Distribution of \textit{IL-16} rs4778889, rs11556218 and rs4072111 genotypes among the 958 patients with oral cancer and 958 controls.

| Genotype | Patients | Controls | OR (95% CI) | \(p\)-Value* |
|----------|----------|----------|-------------|--------------|
|          | n        | %        | n           | %            |
| rs4778889|          |          |             |              |
| TT       | 633      | 66.1%    | 621         | 64.8%        | 1.00 (reference) |
| CT       | 293      | 30.6%    | 302         | 31.5%        | 0.95 (0.78-1.16)  | 0.6198           |
| CC       | 32       | 3.3%     | 35          | 3.7%         | 0.90 (0.55-1.47)  | 0.6647           |
| CT+CC    | 325      | 33.9%    | 337         | 35.2%        | 0.95 (0.78-1.14)  | 0.5643           |
| \(p\)_{\text{trend}}|          |          |             |              |
| rs11556218|         |          |             |              |
| TT       | 633      | 66.1%    | 693         | 72.3%        | 1.00 (reference)  |
| TG       | 269      | 28.1%    | 239         | 25.0%        | \textbf{1.23 (1.00-1.51)} | \textbf{0.0456}* |
| GG       | 56       | 5.8%     | 26          | 2.7%         | \textbf{2.36 (1.46-3.80)} | \textbf{0.0003}* |
| TG+GG    | 325      | 33.9%    | 265         | 27.7%        | \textbf{1.34 (1.11-1.63)} | \textbf{0.0030}* |
| \(p\)_{\text{trend}}|          |          |             |              |
| rs4072111|         |          |             |              |
| CC       | 588      | 61.4%    | 571         | 59.6%        | 1.00 (reference)  |
| CT       | 332      | 34.7%    | 346         | 36.1%        | 0.93 (0.77-1.13)  | 0.4651           |
| TT       | 38       | 3.9%     | 41          | 4.3%         | 0.90 (0.57-1.42)  | 0.6507           |
| CT+TT    | 370      | 38.6%    | 387         | 40.4%        | 0.93 (0.77-1.12)  | 0.4269           |
| \(p\)_{\text{trend}}|          |          |             |              |

n: Number; OR: odds ratio; \(p\)_{\text{trend}}: \(p\)-Value for trend analysis. *Based on Chi-square without Yates’s correction test; the significant \(p\)-Values and odds ratios are bolded and marked with a star.
To validate the interesting findings presented in Table III, we also examined the distribution of the allelic frequencies in IL-16 rs4778889, rs11556218 and rs4072111 in Table IV. In agreement with the findings in Table III, the variant G allele in IL-16 rs11556218 was associated with a significantly elevated oral cancer risk, compared to the wild-type allele T (OR = 1.39, 95% CI = 1.17-1.64, p = 0.0001) (Table IV, middle panel). In detail, the frequencies of the T and G alleles of IL-16 rs11556218 were 80.1% and 19.9% among the oral cancer patients, respectively, and 84.8% and 15.2%, respectively, among the non-cancer age- and gender-matched healthy controls (Table IV, middle panel). On the contrary, neither the variant C allele of IL-16 rs4778889 nor the variant T allele of IL-16 rs4072111 were associated with and altered oral cancer risk (Table IV, top and bottom panels, respectively).

Since oral cancer can be related with the consumption of betel quid chewing in Taiwan, we were very interested in the interaction between the genotype of IL-16 rs11556218 with betel quid chewing behavior and whether such a combination poses an even higher risk for oral cancer. The joint effect of IL-16 rs11556218 with betel quid chewing habit on oral cancer is shown in Table V. All oral cancer patients and age- and gender-matched controls were stratified according to whether they chew betel quid and their IL-16 rs11556218 genotypes. Interestingly, the results showed that there was no higher risk for non-chewers (Table V, top panel); however, there was a significantly elevated oral cancer risk for the betel quid chewers with a variant TG or GG genotypes in IL-16 rs11556218 (p = 0.0013) (Table V, bottom panel).

**Discussion**

In the current study, we examined the contribution of IL-16 genotypes to elevated oral cancer risk among an extremely large population of Taiwanese, containing 958 oral cancer patients and 958 age-, gender-matched healthy controls. The highlight results showed that IL-16 rs11556218 G carriers were of a statistically higher risk for oral cancer, while this significance was not found for the IL-16 rs4778889 or IL-16 rs4072111 alleles. The IL-16 rs11556218 is a polymorphic site in charge of a missense coding from the wild-type Asn (T) to the variant Lys (G). Notably, IL-16 rs11556218 TG and GG genotypes could potentially serve as novel genomic biomarkers for predicting increased oral cancer risk in Taiwan, where the density of oral cancer is the highest in the world. In 2009, the serum levels of IL-16 were reported to be higher in colorectal cancer and gastric cancer patients; however, no significant genotype-phenotype correlation between IL-16 rs11556218 polymorphisms and serum levels of IL-16 was observed in that study (15). There is no literature available about the expression levels of IL-16 among oral cancer patients. Future studies on the specific genotype-phenotype correlation of IL-16 among Taiwanese will provide useful information for predicting those at higher risk.

In our study, we further found that the variant genotypes of IL-16 rs11556218 were associated with an elevated oral cancer risk in the group of betel quid chewers, but not in the...
non-chewers group. These novel findings strongly encourage additional investigations regarding the functional phenotypes of IL-16 rs11556218 and their involvement in oral cancer etiology, as well as the interaction between IL-16 rs11556218 and betel quid chewing.

In the current study, we proposed the variant TG and GG genotypes at IL-16 rs11556218 can serve as practical biomarkers for oral cancer risk prediction in Taiwan. An elevated risk has also been found in several other types of cancer, including nasopharyngeal carcinoma (another important head and neck cancer) (23), gastric cancer (15), hepatocellular carcinoma (24) and colorectal cancer (15) in other populations. It is of great interest for us to investigate whether IL-16 rs11556218 can serve as practical biomarkers for these types of cancer in Taiwan. As for IL-16 rs4778889, it has been found that the C allele of IL-16 rs4778889 is associated with the risk of renal cell carcinoma (25), especially among Asian ethnicities (26); however, this polymorphic site is not a contributor to oral cancer risk prediction.

From the viewpoint of oral cancer genomics, there are several biomarkers in the fields of DNA repair activity (27, 28), extracellular matrix regulation (17, 18), antioxidant capacity (28, 29), cell viability (19). All these, in addition to the immuneresponsiveness studied here, are contributors to differential susceptibility of individual patients. These markers can potentially be correlated with information from the systemic recordings found in clinicopathological databases of the oral cancer patients for the prediction of prognosis outcomes, such as survival (30) and metastasis (31). Additional genotype-phenotype correlation studies can help in revealing the biological meanings of these genomic markers, extending our understanding of the etiology of each oral cancer patient, leading to personalized therapeutic options.

In conclusion, the study provides solid evidence that the TG and GG genotypes of IL-16 rs11556218 are associated with increased oral cancer risk among Taiwanese, especially those with betel quid chewing habit. Further studies with larger subjects in diverse ethnic populations are needed to verify our findings. The genotype-phenotype correlation investigations would be very valuable to reveal the contribution of IL-16 to oral carcinogenesis.

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