Abstract. Background/Aim: Interleukin-16 has been reported to exhibit tumoricidal effects, however, the contribution of IL-16 genotypes to lung cancer is still largely unrevealed. This study aimed at investigating whether IL-16 genotypes contribute to lung cancer susceptibility. Materials and Methods: IL-16 rs4778889, rs11556218, and rs4072111 genotypic characteristics were determined among 358 lung cancer patients and 716 controls via the polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP) methodology. Results: The highlight finding is that the distributions of genotypic (p=8.6E-10) and allelic (p=0.0001) frequencies of IL-16 rs11556218 was significantly different between cases and controls. In detail, the frequencies of IL-16 rs11556218 heterozygous variant TG and homozygous variant GG were 36.6 and 7.3% among the lung cancer patients, significantly higher than those among the controls (22.5% and 2.6%). On the other way, no difference was observed regarding IL-16 rs4778889 or IL-16 rs4072111. Conclusion: The present study indicates IL-16 rs11556218 G allele is significantly associated with increased Taiwan lung cancer risk.

Lung cancer remains a serious public health problem since it has been the leading cause of cancer mortality worldwide (1, 2). Although first-line chemotherapeutic approaches such as paclitaxel (PTX) and cisplatin (CDDP) doublet chemotherapy are effective for non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (3-5), the 5-year survival rates are still very low (6-8). Thus, a better target or marker for advanced precise therapeutic approaches such as immunotherapy is urgently needed. To fulfill this aim, several groups have reported that specific genotypes are associated with increased lung cancer risk for cigarette smokers than non-smokers (9-16) and vice versa (17-20) from genomic investigations. These studies elucidating the contribution of both genomic and behavioral factors to lung cancer etiology may provide better therapeutic decision-making consulting systems for revealing the personalized etiology, precision therapy and genomic pharmacology of lung cancer.

Interleukin-16 (IL-16), a cytokine originally described as lymphocyte chemoattractant factor (LCF) in 1982 (21), is encoded by the IL-16 gene located on chromosome 15q26.3. It is composed of 631 amino acids and further cleaved by caspase 3 to active IL-16 comprising the C-terminal 121 amino acids.
is also examined.

of smoking status and patients with lung cancer history of any other cancer and pulmonary diseases, such as chronic obstructive pulmonary disease (COPD), pneumothorax and asthma, were all excluded. Then, the participants, who were all Taiwanese, were asked to complete a self-administered questionnaire and provide their blood sample for genotyping studies after their agreeing to join this project. Second, twice the number of non-lung cancer healthy volunteers, as controls, were selected by a criterion matching for age, gender and smoking status after an initially random sampling from the Health Examination Cohort of the hospital. Third, the exclusion criteria for the controls included previous malignancy, metastasized cancer from other origin(s), and any well-known genetic or familial diseases. The study has been reviewed and approved by the Institutional Review Board with the document coded DMR100-IRB-284 and the written informed consents were collected from all the subjects in this project. The demographic characteristics such as the age, gender, smoking status and histological types are shown in Table I.

### IL-16 genotyping conditions

Genomic DNA from the peripheral blood leukocytes of each lung cancer patient and control subject was prepared using the QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) (35, 36) and further processed in a typical polymerase chain reaction (PCR) processes as our previous papers (37-39). The designed primer sequences, corresponding restriction enzymes (New England BioLabs, Ipswich, MA, USA) and PCR products after enzyme digestion for IL-16 genotyping identification are shown in Table II. The PCR cycling were set as: 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 agarose gel is 3% and the electrophoresis conditions are 100 Volt for 20 min. The genotyping analysis was conducted by three researchers independently and blindly. For each of the IL-16 SNP investigated in this study, 18 of the cases and 36 of the controls were chosen for direct sequencing. Overall, the genotypes identified by PCR-based RFLP methodology and direct sequencing methodology were one hundred percent concordant to each other.

## Materials and Methods

### Investigated controls and cases

Briefly, three hundred and fifty-eight lung cancer patients were recruited at the China Medical University Hospital in central Taiwan. The demographic indexes of the lung cancer patients, including their histological details, were all graded and defined by expert surgeons led by Dr. Hsia. First, patients with lung cancer history of any other cancer and pulmonary amino acids (22-24). Binding together with CD4 protein, IL-16 is capable to activate CD4+ T cells, monocytes, macrophages, eosinophils, and dendritic cells, and promote their secretion of inflammatory cytokines, such as IL-1b (25), TNF-a, and IL-15 (26). Interestingly, elevated IL-16 levels were observed in several types of cancer tissues both in vitro and in vivo (27-33). Recently, a genome-wide association study reported that IL-16 genotype may be capable to serve as a practical marker for prostate cancer prediction (34). One study indicated that IL-16 rs11556218 T/G was significantly associated with the risk of colorectal cancer and gastric cancer patients (33). In the same study, both male and female patients carrying the G allele had a significantly higher risk for developing colorectal cancer and gastric cancer compared to T allele carriers. Alternatively, women carrying the T allele at IL-16 rs4072111 have a lower risk for colorectal cancer and gastric cancer compared than those carrying the C allele (33).

Despite the significance of IL-16 in cancer pathogenesis, no investigation of the association between IL-16 genotypes and lung cancer has been studied. Based on the highlights above, we aimed at evaluating whether rs4778889 T/C, rs11556218 T/G and rs4072111 C/T polymorphisms of IL-16 are associated with the personal risk to lung cancer in a representative Taiwan population. In addition, the joint effect of smoking status and IL-16 genotypes on lung cancer risk is also examined.

### Statistical analyses

Seven hundred and sixteen of the controls and 358 lung cancer patients with both genotypic and selected characters listed in Table I were analyzed. The Student’s t-test was used to
compare the difference of age between the case and control groups. Typical Pearson’s Chi-square test was adopted for comparisons of the distributions for the IL-16 genotypes between the case and control groups. The associations between the IL-16 genotypes and lung cancer risk were estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs) from logistic regression analysis. Any comparison with \( p < 0.05 \) was considered statistically significant.

### Results

Table I summarizes the demographic characteristics of the 1,074 participants (358 patients with lung cancer and 716 non-cancer healthy controls) in this study. No significant difference on age, gender distribution or smoking and alcohol consumption status was identified between lung cancer and control groups, suggesting that subject matching based on these indexes was successful as we have designed. From the viewpoints of pathological identification, there were 60.9% of lung cancer patients belonging to the adenocarcinoma type, 29.6% of the lung cancer patients belonging to the squamous cell carcinoma type, and 9.5% belonging to other types (Table I).

In Table III, we summarize the distribution of genotypic frequencies of the 3 SNPs (rs4778889, rs11556218 and rs4072111 in IL-16) for all the investigated subjects. First, we investigated the genotypic frequencies for the three SNPs agreed with the Hardy-Weinberg equilibrium in the control group (all \( p > 0.05 \)). Second, noticeably, there is a significant difference in the distribution of IL-16 rs11556218 genotypic frequencies between lung cancer and control groups (\( p = 8.6E-10 \)) (Table III, middle panel), but not for those of IL-16 rs4778889 or IL-16 rs4072111 (both \( p > 0.05 \)) (Table III, top and bottom panels). In detail, the frequencies of the IL-16 rs11556218 heterozygous variant TG and homozygous variant GG were 36.6 and 73.3% among lung cancer patients, are significantly higher compared to those among the healthy controls (22.5% and 2.6%). Thus, the TG (OR=2.17, 95%CI=1.64-2.88, \( p = 0.0001 \)) and GG (OR=3.65, 95%CI=1.98-6.74, \( p = 0.0001 \)) genotype at IL-16 rs11556218 seemed to be a potential biomarker for higher risk of Taiwan lung cancer. Last, we combined the variant TG+GG at IL-16 rs11556218, and examined if the elevated risk for lung cancer risk still exists in this combined genotypes compared with wild-type TT genotype (OR=2.33, 95%CI=1.78-3.04, \( p = 0.0001 \)) (Table III, middle panel).

The distribution of allelic frequencies of the 3 SNPs in IL-16 are analyzed to validate the findings in Table IV. Consistent with the findings in Table III, the variant G allele at IL-16 rs11556218 was associated with a significantly elevated risk of lung cancer, compared to the wild-type allele T (OR=2.13, 95%CI=1.70-2.66, \( p = 0.0001 \)) (Table IV, middle panel). In detail, the frequencies of the T and G alleles of IL-16 rs11556218 were 74.4% and 25.6% among lung cancer patients, respectively, while are 86.1% and 13.9% among the healthy controls (Table IV, middle panel). On the contrary, neither the variant C allele of IL-16 rs4778889 nor variant T allele of IL-16 rs4072111 was associated with lung cancer risk (Table IV, top and bottom parts).

Since lung cancer is one of the smoking behavior-related cancers, we also examined the interaction between the genotype of IL-16 rs11556218 with personal smoking behavior among the investigated subjects. The joint effects of IL-16 rs11556218 genotype with individual smoking status are shown in Table V. The lung cancer patients and matched controls were stratified according to their smoking status. The results showed that there was also a significantly elevated lung cancer risk for those non-smokers with variant TG or GG genotypes at IL-16 rs11556218 (\( p = 0.0022 \)) (Table V, top panel). At the same time, ever smokers carrying variant TG and GG genotypes at IL-16 rs11556218 were at an increased risk of lung cancer (\( p = 2.8E-7 \)) (Table V, bottom panel). There is no joint effect between rs4778889 or IL-16 rs4072111 with smoking on lung cancer risk determination (data not shown).

### Discussion

In the current study, we investigated the association of IL-16 genotypes and lung cancer risk in a moderate population of Taiwanese, containing 358 lung cancer patients and 716 age-, gender- and behavior-matched healthy controls (Table I). The results from PCR-RFLP showed that IL-16 rs11556218 G carriers were of a statistically higher risk for lung cancer...
Tables III and IV. Distribution of IL-16 rs4778889, rs11556218 and rs4072111 genotypes among the 358 lung cancer and the 716 controls.

Table III

| Genotype | Cases | Controls | OR (95% CI) | p-Value
|----------|-------|----------|-------------|--------|
|          | N     | %        | N           | %      |
| rs4778889 |       |          |             |        |
| TT       | 234   | 65.4%    | 456         | 63.7%  | 1.00 (reference) |
| CT       | 113   | 31.5%    | 239         | 33.4%  | 0.92 (0.70-1.21) | 0.5575 |
| CC       | 11    | 3.1%     | 21          | 2.9%   | 1.02 (0.48-2.15) | 0.9570 |
| CT+CC    | 124   | 34.6%    | 260         | 36.3%  | 0.93 (0.71-1.21) | 0.5890 |
| P_{trend} |       |          |             | 0.8353 |
| rs11556218 |      |          |             |        |
| TT       | 201   | 56.1%    | 536         | 74.9%  | 1.00 (reference) |
| TG       | 131   | 36.6%    | 161         | 22.5%  | 2.17 (1.64-2.88) | 0.0001* |
| GG       | 26    | 7.3%     | 19          | 2.6%   | 3.65 (1.98-6.74) | 0.0001* |
| TG+GG    | 157   | 43.9%    | 180         | 25.1%  | 2.33 (1.78-3.04) | 0.0001* |
| P_{trend} |       |          |             | 8.6E-10* |
| rs4072111 |      |          |             |        |
| CC       | 224   | 62.6%    | 441         | 61.6%  | 1.00 (reference) |
| CT       | 117   | 32.7%    | 247         | 34.5%  | 0.93 (0.71-1.22) | 0.6155 |
| TT       | 17    | 4.7%     | 28          | 3.9%   | 1.20 (0.64-2.33) | 0.5746 |
| CT+TT    | 134   | 37.4%    | 275         | 38.4%  | 0.96 (0.74-1.25) | 0.7558 |
| P_{trend} |       |          |             | 0.7157 |

*Based on Chi-square without Yate’s correction test; significant p-values and odds ratios are bolded and marked with an asterisk (*).

Table IV

| Allele | Cases | Controls | OR (95% CI) | p-Value
|--------|-------|----------|-------------|--------|
|        | N     | %        | N           | %      |
| rs4778889 |      |          |             |        |
| Allele C | 135   | 18.9%    | 281         | 19.6%  | 1.03 (0.82-1.30) | 0.7706 |
| Allele T | 533   | 74.4%    | 1233        | 86.1%  | 1.00 (reference) |
| Allele G | 183   | 25.6%    | 199         | 13.9%  | 2.13 (1.70-2.66) | 0.0001* |
| Allele C | 565   | 78.9%    | 1229        | 78.8%  | 1.00 (reference) |
| Allele T | 151   | 21.1%    | 303         | 21.2%  | 1.08 (0.87-1.35) | 0.4706 |

*Based on Chi-square without Yate’s correction test; the significant p-value and odds ratio are bolded and marked with an asterisk (*).

(Table III and IV). Thus, IL-16 rs11556218 TG and GG genotypes, but not any genotype at IL-16 rs4778889 or IL-16 rs4072111 (Table III), were novel genomic biomarkers for prediction of elevated lung cancer risk in Taiwan. We further found that variant genotypes of IL-16 rs11556218 were associated with elevated lung cancer risk among not only non-smoker but smoker subgroups (Table V). These findings support the concept that functional polymorphisms of IL-16 involve in the lung cancer etiology.

The first SNP rs4778889 is an intronic polymorphic site, whose variations seemed not to contribute to altered lung cancer risk from the results (Tables III and IV). The third SNP rs4072111 is a polymorphic site in charge of a missense coding from wild-type Pro (C) to variant Ser (T), whose genetic variations seem not to contribute to altered lung cancer risk (Tables III and IV). The highlight findings focus on the second SNP rs11556218 we checked, which is also a polymorphic site in charge of a missense coding from wild-type Asn (T) to variant Lys (G). The results show that the variant G allele at IL-16 rs11556218 was associated with a significantly elevated risk of lung cancer, compared to the wild-type allele T (Table IV). In the literature, serum levels of IL-16 were reported to be higher in colorectal cancer and gastric cancer patients (33). However, no significant genotype-phenotype correlation between IL-16 rs11556218 polymorphisms and serum levels of IL-16 was observed in that study (33).

In the current study, we proposed a practical biomarker, the TG and GG genotypes at IL-16 rs11556218, for lung cancer prediction in Taiwan (Tables III and IV). The elevated risk was also found in several types of cancers including gastric cancer (33), colorectal cancer (33), HBV-related hepatocellular carcinoma (40) and nasopharyngeal carcinoma (41).

The genotype of IL-16 rs4778889 was found to be associated with the risk of renal cell carcinoma (42). In the most updated meta-analysis of IL-16 genotype and cancer, the C allele at IL-16 rs4778889 was found to significantly correlate with higher renal cell carcinoma risk, especially among Asian ethnicities (43). Different from those findings mentioned above, genotypes of IL-16 rs11556218 were not associated with the risk of the risk of renal cell carcinoma, and the mechanisms need further validation.

Since lung cancer is one of the smoking-related cancers, the interaction of the genotype of IL-16 rs11556218 and cigarette smoking status for the participants is further analyzed after we have revealed its contribution to lung
cancer susceptibility in Table V. The results showed that the genotypic distribution of the variant genotypes of IL-16 rs11556218 was significantly different between lung cancer and control sub-groups both with and without the cigarette smoking habits (Table V). At the same time, there is no differential distribution observed for the genotypes of IL-16 rs4778889 nor rs4072111 among neither smokers nor non-smokers (data not shown). As for the gender difference, Gao and colleagues reported that both male and female patients carrying the G allele had a significantly higher risk for developing colorectal cancer and gastric cancer compared to individuals carrying the T allele (33). Their findings are similar to ours that no gender difference on the significance for IL-16 rs11556218 genotypes was observed. We also analyzed the interaction of the IL-16 rs11556218 genotype with age and alcohol drinking status finding that the interactions were significant both among younger and elderly groups, and also both in drinker and non-drinker groups (data not shown). Thus, the marker IL-16 rs11556218 is practically useful for lung cancer prediction among Taiwanese for both genders, and for those with or without smoking or alcohol drinking habits.

From the pathobiological viewpoint, the elevated levels of serum IL-16 have been found in metastatic cancers and correlated with poorer prognosis of several types of cancer including breast cancer, gastrointestinal cancer, renal cancer, ovarian cancer and myeloma (44, 45). Those SNPs on IL-16 such as rs11556218 have been reported to associate with risk to gastric cancer (46), colorectal cancer (46), prostate cancer (47) and renal cancer (48). Donati and colleagues demonstrated that IL-16 plays a role in early steps of lung cancer cell metastasis (49). In 2017, Pérez-Ramírez and colleagues reported that the variant GG genotypes at IL-16 rs7170924 could serve as a predictive marker for higher risk of death (50). In the current study, neither IL-16 rs11556218, rs4778889 nor rs4072111 could serve as a predictive marker for poorer prognosis of lung cancer in the aspects of metastasis or death risk (data not shown).

In conclusion, this study provides evidence that the TG and GG genotypes of IL-16 rs11556218 are associated with increased lung cancer risk among Taiwanese, no matter whether being with or without a personal smoking habit. Further studies with larger subject numbers from diverse ethnic populations are needed to verify our findings, in which potential gene-gene and gene-environmental interactions on lung cancer risk validations would be very valuable.

Conflicts of Interest
All the Authors declare no conflicts of interest regarding this study.

Authors’ Contributions
Research design: Wu MF, Tsai CW; patient and questionnaire summaries: Shen TC, Hsia TC; experimental work: Wang YC, Chang WS, Li HT; statistical analysis: Liao CH, Gong CL, Wang ZH; manuscript writing: Tsai CW, Bau DT; review & revision: Bau DT, Chang WS, Tsai CW.

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