Association between IL-17A G197A polymorphism and gastric cancer risk: an updated meta-analysis based on 6,624 cases and 7,631 controls

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Purpose: Previous studies investigating the association between interleukin-17A (IL-17A) G197A polymorphism and gastric cancer risk have provided inconsistent results. We, therefore, conducted this meta-analysis to clarify the association between IL-17A G197A polymorphism and gastric cancer risk.

Methods: We searched PubMed, Excerpta Medica Database, and CNKI databases to identify relevant studies up to June 10, 2017. A total of 16 case-control studies including 6,624 cases and 7,631 controls were identified.

Results: Overall, significant associations between IL-17A G197A polymorphism and gastric cancer risk were observed (A vs G: OR = 1.24, 95% CI = 1.14–1.36; AA vs GG: OR = 1.63, 95% CI = 1.35–1.96; GA vs GG: OR = 1.12, 95% CI = 1.01–1.25; AA+GA vs GG: OR = 1.23, 95% CI = 1.11–1.35; AA vs GA+GG: OR = 1.54, 95% CI = 1.27–1.87). Similar associations were also observed in Asian population (A vs G: OR = 1.25, 95% CI = 1.15–1.37; AA vs GG: OR = 1.62, 95% CI = 1.33–1.97; GA vs GG: OR = 1.16, 95% CI = 1.07–1.25; AA+GA vs GG: OR = 1.24, 95% CI = 1.15–1.33; AA vs GA+GG: OR = 1.51, 95% CI = 1.23–1.85), in Caucasian population (AA vs GA+GG: OR = 2.19, 95% CI = 1.40–3.44), and in the hospital-based controls’ subgroup (A vs G: OR = 1.30, 95% CI = 1.17–1.45; AA vs GG: OR = 1.81, 95% CI = 1.46–2.25; AA+GA vs GG: OR = 1.27, 95% CI = 1.12–1.43; AA vs GA+GG: OR = 1.71, 95% CI = 1.34–2.18).

Conclusions: The current meta-analysis suggests that IL-17A G197A polymorphism might enhance gastric cancer risk.

Keywords: gastric cancer, polymorphism, meta-analysis, interleukin-17A, rs2275913

Introduction

Interleukin-17 (IL-17) is a relatively newly described family of pro-inflammatory cytokines that consists of six family members (IL-17A–F).¹ IL-17 is produced by CD4⁺ memory T cells, and it is involved in both innate and adaptive immune responses.²,³ It has been reported that IL-17A, a pro-inflammatory cytokine, is associated with the pathogenesis of chronic inflammatory diseases, autoimmune diseases,⁴,⁵ and cancer progression.⁶,⁷

There are many studies that focus on the relationship between IL-17A G197A polymorphism and gastric cancer.³–²³ These studies are all based on experimental results, but their results are always inconsistent. Since 2015, only one meta-analysis has been conducted, and 11 case-control studies were included in this meta-analysis.²⁴ Today, more than five studies that assessed the association between IL-17A G197A polymorphism and the risk of gastric cancer have been published. Therefore, we performed
an updated meta-analysis to further determine an accurate relationship between IL-17A G197A polymorphism and gastric cancer susceptibility.

Materials and methods
Publication search
We conducted a publication search in PubMed, Excerpta Medica Database, and CNKI databases (up to June 10, 2017) using the following search strategy: “interleukin-17A or interleukin 17A or IL-17A or IL17A”, “polymorphism”, and “gastric cancer”. No language restrictions were applied. Studies had to meet the following criteria: 1) case-control studies; 2) diagnoses of all patients with malignant tumors were confirmed by pathological or histological examination; 3) the study assessed the association between gastric cancer risk and the IL-17A G197A polymorphism. The following exclusion criteria were used: 1) unpublished studies or abstracts; 2) duplicate publications; and 3) insufficient data were reported.

Data extraction
For each study, the following characteristics were extracted: first author, year of publication, ethnicity, sample size (total cases and controls), source of controls, genotype distributions in cases and controls, and $P$-value of Hardy–Weinberg equilibrium (HWE). Disagreements were resolved by discussion.

Statistical analysis
Odds ratios (ORs) with corresponding 95% CIs were calculated to clarify the strength of the association between IL-17A G197A polymorphism and gastric cancer risk. Five genetic models were assessed: homozygote model (AA vs GG), heterozygote model (GA vs GG), recessive model (AA vs GA+GG), dominant model (AA+GA vs GG), and allele model (A vs G). Subgroup analyses were conducted according to ethnicity and source of controls.

Heterogeneity was calculated by using both $\chi^2$-based $Q$-statistic and $F$-statistic. If $P$>0.1 and $F<$50%, the fixed-effects model (Mantel–Haenszel method) was chosen. Otherwise, the random effects model (Der Simonian–Laird method) was used. Moreover, sensitivity analysis was performed to assess the stability of the results. Publication bias was assessed with funnel plots and Egger’s test. All of the statistical tests were carried out with STATA version 12.0 (StaCorp corporation, College Station, TX, USA). $P<$0.05 was considered significant, and all $P$-values were two sided.

Results
Characteristics of eligible studies
A flow diagram illustrating the study selection process is shown in Figure 1. Through literature search and selection, a total of 16 publications including 6,624 cases and 7,631 controls were included in the meta-analysis. Table 1 shows the main characteristics of the included studies.

Meta-analysis
Overall, the IL-17A G197A polymorphism was associated with an increased gastric cancer risk in all genetic models (A vs G: OR =1.24, 95% CI =1.14–1.36, Figure 2; AA vs GG: OR =1.63, 95% CI =1.35–1.96, Figure 3; GA vs GG: OR =1.12, 95% CI =1.01–1.25, Figure 4; AA+GA vs GG: OR =1.23, 95% CI =1.11–1.35, Figure 5; AA vs GA+GG: OR =1.54, 95% CI =1.27–1.87, Figure 6). The HWE of each study was taken into consideration. After eliminating studies whose distribution of genotype in controls deviated from HWE, the outcome remained statistically significant. These results are shown in Table 2.

When subgroup analysis was carried out based on ethnicity, significant associations were found in all five genetic models in Asian population (A vs G: OR =1.25, 95% CI =1.15–1.37; AA vs GG: OR =1.62, 95% CI =1.33–1.97; GA vs GG: OR =1.16, 95% CI =1.07–1.25; AA+GA vs GG: OR =1.24, 95% CI =1.15–1.33; AA vs GA+GG: OR =1.51, 95% CI =1.23–1.85), and statistically significant
associations were found in the following genetic model in Caucasian population (AA vs GA+GG: OR = 2.19, 95% CI = 1.40–3.44).

When results were stratified by source of controls, IL-17A G197A polymorphism was associated with a significantly increased gastric cancer risk in the hospital-based controls’ subgroup (A vs G: OR = 1.30, 95% CI = 1.17–1.45; AA vs GG: OR = 1.81, 95% CI = 1.46–2.25; AA+GA vs GG: OR = 1.27, 95% CI = 1.12–1.43; AA vs GA+GG: OR = 1.71, 95% CI = 1.34–2.18). However, no associations were

### Table 1 Characteristics of studies included in the meta-analysis

| Author               | Year | Ethnicity | Source of controls | Cases | Controls | Case   | Control   | HWE |
|----------------------|------|-----------|-------------------|-------|----------|--------|-----------|-----|
| Shibata et al⁶        | 2009 | Asian     | Hospital-based    | 287   | 523      | 94     | 124       | 69  | 175 | 299 | 49 | <0.001 |
| Chen¹⁷               | 2010 | Asian     | Population-based  | 1,042 | 1,090    | 300    | 522       | 220 | 325 | 541 | 224 | 0.967  |
| Wu et al⁹            | 2010 | Asian     | Population-based  | 945   | 768      | 210    | 485       | 250 | 193 | 371 | 204 | 0.351  |
| Arisawa et al¹⁰      | 2012 | Asian     | Hospital-based    | 333   | 583      | 112    | 137       | 84  | 218 | 293 | 72  | 0.08   |
| Rafiei et al¹¹       | 2013 | Caucasian | Population-based  | 161   | 171      | 56     | 61        | 44  | 78  | 72  | 21  | 0.491  |
| Qinghai et al¹²      | 2014 | Asian     | Hospital-based    | 293   | 550      | 126    | 122       | 45  | 273 | 216 | 61  | 0.069  |
| Kutukhin et al¹³      | 2014 | Caucasian | Population-based  | 60    | 300      | 24     | 26        | 10  | 99  | 165 | 36  | 0.009  |
| Gonzalez-Hormazabal et al¹⁴ | 2014 | Mixed     | Hospital-based    | 147   | 172      | 103    | 36        | 8   | 105 | 59  | 8   | 0.937  |
| Wang et al¹⁵         | 2014 | Asian     | Hospital-based    | 462   | 462      | 160    | 211       | 91  | 214 | 190 | 58  | 0.124  |
| Zhang et al¹⁶        | 2014 | Asian     | Population-based  | 260   | 312      | 110    | 102       | 48  | 258 | 187 | 67  | <0.001 |
| Wu et al¹⁷           | 2014 | Asian     | Hospital-based    | 945   | 768      | 210    | 485       | 250 | 193 | 371 | 204 | 0.351  |
| Gao et al¹⁸          | 2015 | Asian     | Hospital-based    | 572   | 573      | 239    | 250       | 83  | 260 | 241 | 72  | 0.17   |
| Hou and Yang²⁰       | 2015 | Asian     | Hospital-based    | 326   | 326      | 121    | 149       | 56  | 161 | 136 | 29  | 0.001  |
| Qi et al²¹           | 2015 | Asian     | Hospital-based    | 252   | 252      | 100    | 110       | 42  | 122 | 105 | 25  | 0.73   |
| Yang et al²²         | 2016 | Asian     | Hospital-based    | 386   | 374      | 200    | 128       | 58  | 203 | 123 | 48  | <0.001 |
| Zhao et al²³         | 2016 | Asian     | Hospital-based    | 153   | 207      | 51     | 76        | 26  | 95  | 94  | 18  | 0.437  |

Abbreviation: HWE, Hardy–Weinberg equilibrium.

### Figure 2 Forest plot of the association between IL-17A G197A polymorphism and gastric cancer risk in the allele model (A vs G) among the overall populations.

Note: Weights are from random effects analysis.

Abbreviations: IL, interleukin; OR, odds ratio.
### Figure 3
Forest plot of the association between IL-17A G197A polymorphism and gastric cancer risk in the homozygote model (AA vs GG) among the overall populations.

**Note:** Weights are from random effects analysis.

**Abbreviations:** IL, interleukin; OR, odds ratio.

### Table

| Study ID                  | OR (95% CI) | % weight |
|--------------------------|-------------|----------|
| Shibata et al\(a\)       | 2.62 (1.68–4.09) | 6.51     |
| Chen\(17\)               | 1.06 (0.83–1.36)  | 8.80     |
| Wu et al\(b\)            | 1.13 (0.86–1.47)  | 8.51     |
| Arisawa et al\(10\)      | 2.27 (1.54–3.35)  | 7.13     |
| Rafiei et al\(11\)       | 2.92 (1.57–5.44)  | 4.78     |
| Qinghai et al\(12\)      | 1.60 (1.03–2.48)  | 6.56     |
| Kutikhin et al\(13\)     | 1.15 (0.50–2.63)  | 3.37     |
| Gonzalez-Hornazabal et al\(14\) | 1.02 (0.37–2.82) | 2.52     |
| Wang et al\(15\)         | 2.10 (1.42–3.09)  | 7.14     |
| Zhang et al\(16\)        | 1.68 (1.09–2.59)  | 6.63     |
| Wu et al\(18\)           | 1.13 (0.86–1.47)  | 8.51     |
| Gao et al\(19\)          | 1.25 (0.87–1.80)  | 7.44     |
| Hou and Yang\(20\)       | 2.57 (1.55–4.26)  | 5.85     |
| Qi et al\(21\)           | 2.05 (1.17–3.59)  | 5.32     |
| Yang et al\(22\)         | 1.23 (0.80–1.88)  | 6.67     |
| Zhao et al\(23\)         | 2.69 (1.35–5.37)  | 4.26     |
| Overall (P=66.9%, P=0.000) | 1.63 (1.35–1.96) | 100      |

### Figure 4
Forest plot of the association between IL-17A G197A polymorphism and gastric cancer risk in the heterozygote model (GA vs GG) among the overall populations.

**Note:** Weights are from random effects analysis.

**Abbreviations:** IL, interleukin; OR, odds ratio.

### Table

| Study ID                  | OR (95% CI) | % weight |
|--------------------------|-------------|----------|
| Shibata et al\(a\)       | 0.77 (0.56–1.07) | 6.20     |
| Chen\(17\)               | 1.05 (0.86–1.27)  | 10.09    |
| Wu et al\(b\)            | 1.20 (0.95–1.52)  | 8.68     |
| Arisawa et al\(10\)      | 0.91 (0.67–1.23)  | 6.72     |
| Rafiei et al\(11\)       | 1.18 (0.73–1.91)  | 3.59     |
| Qinghai et al\(12\)      | 1.22 (0.90–1.66)  | 6.69     |
| Kutikhin et al\(13\)     | 0.65 (0.35–1.19)  | 2.48     |
| Gonzalez-Hornazabal et al\(14\) | 0.62 (0.38–1.02) | 3.46     |
| Wang et al\(15\)         | 1.49 (1.12–1.97)  | 7.29     |
| Zhang et al\(16\)        | 1.28 (0.92–1.78)  | 6.15     |
| Wu et al\(18\)           | 1.20 (0.95–1.52)  | 8.68     |
| Gao et al\(19\)          | 1.13 (0.88–1.45)  | 8.31     |
| Hou and Yang\(20\)       | 1.46 (1.05–2.03)  | 6.09     |
| Qi et al\(21\)           | 1.28 (0.88–1.86)  | 5.17     |
| Yang et al\(22\)         | 1.06 (0.77–1.45)  | 6.47     |
| Zhao et al\(23\)         | 1.51 (0.96–2.37)  | 3.94     |
| Overall (P=41.9%, P=0.040) | 1.12 (1.01–1.25) | 100      |
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Figure 5 Forest plot of the association between IL-17A G197A polymorphism and gastric cancer risk in the dominant model (AA+GA vs GG) among the overall populations.

Note: Weights are from random effects analysis.

Abbreviations: IL, interleukin; OR, odds ratio.

Figure 6 Forest plot of the association between IL-17A G197A polymorphism and gastric cancer risk in the recessive model (AA vs GA+GG) among the overall populations.

Note: Weights are from random effects analysis.

Abbreviations: IL, interleukin; OR, odds ratio.
observed in population-based controls’ subgroup in all five comparison models. All comparisons are listed in Table 2.

**Sensitivity analysis and publication bias**

Sensitivity analyses showed that omitting an individual study from all the analyses did not affect the pooled ORs significantly and no substantial change was detected, indicating that the overall results of the present study are stable (Figure 7).

Begg’s funnel plot was used to assess the publication bias of included literature. The shapes of the funnel plots did not show any evidence of obvious asymmetry, indicating the absence of publication bias (Figure 8).

**Discussion**

Genetic and environmental factors, lifestyle, and *Helicobacter pylori* infections have been considered as playing essential roles in the development of gastric cancer, but the precise etiology of the disease remains inconsistent.

IL-17 is a critical inflammatory cytokine that plays an important role in chronic inflammation, autoimmune diseases, and cancer. The IL-17A G197A is located in the 5′ region near the *IL-17A* gene, and it may regulate the gene transcription. A previous study has conflicting results about the association between IL-17A G197A polymorphism and gastric cancer risk, which may be because of relatively small sample size and different genetic background. Meta-analysis is a powerful method to evaluate gene–disease associations, by collecting all available published studies to obtain more precise results.

With the development of molecular epidemiology, numerous studies explored the effects of IL-17A G197A polymorphism on gastric cancer susceptibility. In 2014, Yu et al carried out a meta-analysis and revealed that the IL-17A G197A polymorphism was associated with a significantly increased gastric cancer risk. In their work, they identified only six case-control studies evaluating the

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**Table 2 Meta-analysis of the IL-17A polymorphism and gastric cancer risk**

| Groups and subgroups | Comparison | Test of association | Test of heterogeneity |
|----------------------|------------|---------------------|----------------------|
|                      |            | OR  | 95% CI  | P-value | P-value | I² (%) |
| Total studies        | A vs G     | 1.24 | 1.14–1.36 | 0.000   | 0.000   | 67.0   |
|                      | AA vs GG   | 1.63 | 1.35–1.96 | 0.000   | 0.000   | 66.9   |
|                      | GA vs GG   | 1.12 | 1.01–1.25 | 0.030   | 0.040   | 41.9   |
|                      | AA+GA vs GG| 1.23 | 1.11–1.35 | 0.000   | 0.027   | 44.8   |
|                      | AA vs GA+GG| 1.54 | 1.27–1.87 | 0.000   | 0.000   | 76.3   |
| HWE (yes)            | A vs G     | 1.23 | 1.10–1.37 | 0.000   | 0.000   | 71.4   |
|                      | AA vs GG   | 1.56 | 1.26–1.94 | 0.000   | 0.000   | 68.4   |
|                      | GA vs GG   | 1.15 | 1.05–1.25 | 0.002   | 0.160   | 30.0   |
|                      | AA+GA vs GG| 1.23 | 1.10–1.38 | 0.000   | 0.050   | 45.3   |
|                      | AA vs GA+GG| 1.44 | 1.16–1.78 | 0.001   | 0.000   | 75.0   |
| Ethnicity            | Asian      | A vs G     | 1.25 | 1.15–1.37 | 0.000   | 0.001   | 65.0   |
|                      | AA vs GG   | 1.62 | 1.33–1.97 | 0.000   | 0.000   | 69.8   |
|                      | GA vs GG   | 1.16 | 1.07–1.25 | 0.000   | 0.160   | 28.3   |
|                      | AA+GA vs GG| 1.24 | 1.15–1.33 | 0.000   | 0.169   | 27.4   |
|                      | AA vs GA+GG| 1.51 | 1.23–1.85 | 0.000   | 0.000   | 79.0   |
|                      | Caucasian  | A vs G     | 1.30 | 0.73–2.32 | 0.377   | 0.023   | 80.7   |
|                      | AA vs GG   | 1.91 | 0.77–4.75 | 0.166   | 0.078   | 67.9   |
|                      | GA vs GG   | 0.94 | 0.64–1.37 | 0.743   | 0.133   | 55.8   |
|                      | AA+GA vs GG| 1.10 | 0.53–2.31 | 0.797   | 0.040   | 76.3   |
|                      | AA vs GA+GG| 2.19 | 1.40–3.44 | 0.001   | 0.213   | 35.4   |
| Source of controls   | Hospital-based | A vs G     | 1.30 | 1.17–1.45 | 0.000   | 0.001   | 63.8   |
|                      | AA vs GG   | 1.81 | 1.46–2.25 | 0.000   | 0.002   | 62.7   |
|                      | GA vs GG   | 1.13 | 0.99–1.29 | 0.067   | 0.031   | 48.1   |
|                      | AA+GA vs GG| 1.27 | 1.12–1.43 | 0.000   | 0.040   | 46.1   |
|                      | AA vs GA+GG| 1.71 | 1.34–2.18 | 0.000   | 0.000   | 75.2   |
|                      | Population-based | A vs G     | 1.08 | 0.99–1.17 | 0.078   | 0.184   | 37.9   |
|                      | AA vs GG   | 1.16 | 0.99–1.37 | 0.073   | 0.341   | 10.4   |
|                      | GA vs GG   | 1.10 | 0.97–1.26 | 0.147   | 0.215   | 32.8   |
|                      | AA+GA vs GG| 1.12 | 0.99–1.28 | 0.070   | 0.205   | 34.6   |
|                      | AA vs GA+GG| 1.07 | 0.93–1.23 | 0.317   | 0.272   | 23.1   |

Abbreviations: IL, interleukin; OR, odds ratio; HWE, Hardy–Weinberg equilibrium.
association between the IL-17A G197A polymorphism and gastric cancer risk. In 2015, Li et al.24 conducted a meta-analysis to assess the association between IL-17A G197A polymorphism and gastric cancer susceptibility with 11 case-control studies and revealed that IL-17A G197A polymorphism was associated with gastric cancer risk. Therefore, we collected all available published literature and performed an updated meta-analysis of 16 independent case-control studies containing 6,624 cases and 7,631 controls. In the meta-analysis, significant associations between IL-17A G197A polymorphism and gastric cancer risk were observed in all five genetic models. The HWE of each study was taken into consideration. After eliminating studies whose distribution of genotype in controls deviated from HWE, the outcome remained statistically significant. Similar associations were also observed in Asian population (A vs G: OR = 1.25, 95% CI = 1.15–1.37; AA vs GG: OR = 1.62, 95% CI = 1.33–1.97; GA vs GG: OR = 1.16, 95% CI = 1.07–1.25; AA+GA vs GG: OR = 1.24, 95% CI = 1.15–1.33; AA vs GA+GG: OR = 1.51, 95% CI = 1.23–1.85), in Caucasian population (AA vs GA+GG: OR = 2.19, 95% CI = 1.40–3.44), and in the hospital-based controls’ subgroup (A vs G: OR = 1.30, 95% CI = 1.17–1.45; AA vs GG: OR = 1.81, 95% CI = 1.46–2.25; AA+GA vs GG: OR = 1.27, 95% CI = 1.12–1.43; AA vs GA+GG: OR = 1.71, 95% CI = 1.34–2.18).

Several limitations need to be addressed. First, due to heterogeneity, the results of our meta-analysis should be interpreted. Second, the overall outcomes were based on unadjusted ORs. Lacking the information on detailed individual data limited our more precise analysis on adjusted estimates by other factors like age and sex. This limitation may cause serious confounding bias. Third, meta-analysis is a type of retrospective study, and recall and selection bias may be present.

In conclusion, our meta-analysis revealed that IL-17A G197A polymorphism may increase gastric cancer risk. However, larger studies are still required to assess the
interaction of IL-17A G197A polymorphism with gastric cancer risk.

Disclosure
The authors report no conflicts of interest in this work.

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