Contribution of interaction between genetic variants of interleukin-11 and Helicobacter pylori infection to the susceptibility of gastric cancer

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Background: Gastric cancer (GC) ranks the second leading cause of cancer-related mortality worldwide. We aimed to clarify the relevance of genetic variants of IL-11, a hub of various carcinogenic pathways, as well as their interactions with Helicobacter pylori (H. pylori) infection in the development of GC.

Methods: A case-control study with 880 GC cases and 900 healthy controls was conducted in a Chinese population. Six tagSNPs were detected by Taqman Allelic Discrimination assay, while H. pylori status was detected by Typing Detection Kit for Antibody to H. pylori and serum IL-11 level was measured using ELISA method.

Results: We found that rs1126760 (C vs T: OR=1.39, 95% CIs=1.13–1.70, P=0.002) and rs1126757 (C vs T: OR=0.82, 95% CIs=0.72–0.93, P=0.002) were significantly associated with susceptibility of GC. Even adjusted for Bonferroni correction, the results were still significant (P=0.002×6=0.012). IL-11 rs1126760 was significantly associated with higher serum and expression level of IL-11, while rs1126757 was significantly associated with lower serum IL-11 level (P<0.001). Significant interaction with H. pylori infection was identified for rs1126760 (P for interaction =0.005). Higher expression of the IL-11 gene was significant with development and poor prognosis of GC.

Conclusion: Our study provides strong evidence that genetic variants of the IL-11 gene may interact with H. pylori infection and contribute to the development of GC. Further studies with larger sample size and functional experiments are needed to validate our findings.

Keywords: gastric cancer, polymorphism, IL-11, Helicobacter pylori

Introduction

Gastric cancer (GC) ranks the second leading cause of cancer-related mortality as well as the fourth most common cancer globally.1,2 Although the largest statistically significant decreases occurred for GC (decrease of 17.1–11% deaths per 100 000) worldwide, it was estimated that 8,65,000 (8,48,300–8,84,700) deaths occurred annually.3 Especially in China, according to the report of Cancer Statistics in China, 2015, 6,79,100 new GC cases and 4,98,000 deaths happened every year, ranking both the second most common cancer and the second leading cause of cancer-related mortality.4 Diet and Helicobacter pylori (H. pylori) infection have been thought to be the important risk factors for GC.5 Besides, genetic factors have also been identified to be associated with susceptibility of GC, and many loci have been identified through genetic epidemiology studies.6–11
IL-11, a group of cytokines expressed by leukocytes and a member of the IL-6 family of cytokines, regulates tumor-associated inflammation and tumorigenesis making them attractive clues for cancer prevention and targets for adjuvant treatment in cancers. Among them, IL-11 drives gastric tumorigenesis independent of trans-signaling and acts as a hub of various carcinogenic pathways. Many oncogenes and tumor suppressor genes function in the process of gastric carcinogenesis, development, invasion and progression through IL-11.15–22 It could promote chronic gastric inflammation and contribute to tumorigenesis mediated by excessive activation of signal transducers and activators of transcription 3 (STAT3) and signal transducers and activators of transcription 1 (STAT1).20 Genetic variants of the IL-11 gene might affect its gene expression and are associated with multiple diseases, including cancers, chronic obstructive pulmonary disease, ulcerative colitis, osteoarthritis, repeated implantation failure and pregnancy loss.23–30 However, no studies have evaluated the effect of IL-11 polymorphisms on development of GC. In this case-control study, we investigated the genetic associations and interactions between genetic variants of IL-11 and H. pylori infection in the development of GC in a Chinese population.

Patients and methods

Study subjects
Totally included in this study were 880 histologically diagnosed GC patients who were recruited between July 2010 and July 2017. None of the included patients had either a previous history of tumors or a history of chemotherapy and radiotherapy. Nine hundred age- and gender matched-cancer-free controls who had no clinical history of gastroduodenal disease were randomly selected from the subjects who visited the health checkup clinics. Demographic and clinical data were collected from medical records, while 5 mL venous blood was collected from all subjects for analyzing their genetic variations and the H. pylori infection status. The study protocol was approved by the Ethics Committee of People’s Hospital of Jiangxi Province and conducted in compliance with the Declaration of Helsinki. All participants provided written informed consent.

TagSNP selection and genotyping
TagSNPs of the IL-11 gene were selected using Haplovie 4.2 based on the 1000 Genomes Project database (http://www.1000genomes.org) with minor allele frequency >0.05 in the Chinese population as well as a threshold of $r^2$>0.8. Thus, six SNPs, including rs1042505, rs1126760, rs7250912, rs4252556, rs8104023 and rs1126757, were finally selected in the current study. Genomic DNA was isolated from peripheral blood using the QIAGen DNA Blood Maxi Kit (Qiagen, Hilden, Germany) according to the manufacturer’s protocol. Genotyping for all the six SNPs was carried out by Taqman Allelic Discrimination assay using the Quantstudio 12 Kflex (Applied Biosystems, Foster City, CA). Ten percent randomly selected samples were detected in duplicates and the concordance rate was 100%. All laboratory personnel were blinded to the disease status of the study subjects.

H. pylori infection multiplex serology and serum IL-11 assay
We determined the serostatus of antibodies to four H. pylori specific antigens (CagA, VacA, UreA and UreB) using Typing Detection Kit for Antibody to H. pylori (Shenzhen Blot Biotech Co., Ltd, Shenzhen, China) according to the manufacturer’s instructions. The H. pylori seropositivity was defined as any of the positivity of the four antigens. The serum IL-11 levels of 100 randomly selected controls were measured using enzyme-linked immunosorbent assay (ELISA) method.

Bioinformatics analysis
The comparison of expression of IL-11 gene in GC tissues was analyzed using GEPIA.31 The association of expression of the IL-11 gene survival of GC was analyzed using Kaplan–Meier plotter.32 The genotype-based mRNA expression analysis of IL-11 was conducted using GTEx portal (https://www.gtexportal.org/) as described previously.33,34

Statistical analysis
The proportions of selected variables in GC cases and healthy controls were compared by the $\chi^2$ test. Hardy–Weinberg equilibrium (HWE) was evaluated by Pearson’s goodness-of-fit Chi-square ($\chi^2$) test for all tagSNPs. The OR and 95% CI were calculated to evaluate the associations between the genetic variants of the IL-11 gene and GC risk by logistic analysis adjusted for age, gender, smoking and drinking status, H. pylori infection, and education level. The false-positive report probability (FPRP) was calculated to evaluate the significant findings as previously.35 We set 0.2 as an FPRP threshold and assigned a prior probability of 0.1 to detect an OR of 0.67/1.50 (protective/risk effects). FPRP value less than 0.2 was considered a noteworthy finding. Gene–environmental interactions in GC were
tested on multiplicative scales using a likelihood ratio test. All statistical analyses were performed using Stata 12.0 software (StataCorp, College Station, TX, USA). All statistical tests were two-tailed, and a threshold for significance was set at \( P<0.05 \).

**Results**

**Characteristics of the study population**

A total of 880 GC cases and 900 healthy controls were enrolled in this case–control study, respectively. As shown in Table 1, we presented the distributions of selected variables in GC cases and healthy controls. Age and gender were comparable, which means the credibility of the matching effect between the two groups. Compared with the healthy controls, GC cases are more likely to be smokers, drinkers, *H. pylori* carriers, and have a lower education level.

**Table 1** Distributions of selected variables in GC cases and healthy controls

| Characteristic          | Cases (n=880) | Controls (n=900) | \( P \)-value |
|-------------------------|--------------|-----------------|--------------|
| Age                     |              |                 |              |
| <50                     | 401 (45.6%)  | 431 (47.9%)     | 0.327        |
| ≥50                     | 479 (54.4%)  | 469 (52.1%)     |              |
| Gender                                                               |
| Male                    | 574 (65.3%)  | 603 (67.0%)     | 0.429        |
| Female                  | 306 (34.7%)  | 297 (33.0%)     |              |
| Smoking status          |              |                 |              |
| Yes                     | 307 (34.9%)  | 272 (30.2%)     | 0.036        |
| No                      | 573 (65.1%)  | 628 (69.8%)     |              |
| Drinking status         |              |                 | <0.001       |
| Yes                     | 320 (36.4%)  | 181 (20.1%)     |              |
| No                      | 560 (63.6%)  | 719 (79.9%)     |              |
| HP infection            |              |                 | <0.001       |
| Yes                     | 662 (75.2%)  | 460 (51.1%)     |              |
| No                      | 218 (24.8%)  | 440 (48.9%)     |              |
| Education level         |              |                 | <0.001       |
| <High school            | 585 (66.5%)  | 395 (43.9%)     |              |
| ≥High school            | 295 (33.5%)  | 505 (56.1%)     |              |
| Tumor site              |              |                 |              |
| Cardia                  | 285 (32.4%)  | 595 (67.6%)     |              |
| Non-cardia              | 595 (67.6%)  | 285 (32.4%)     |              |
| TNM stages              |              |                 |              |
| I                       | 131 (14.9%)  | 157 (17.8%)     |              |
| II                      | 157 (17.8%)  | 407 (46.3%)     |              |
| III                     | 407 (46.3%)  | 185 (21.0%)     |              |

**Note:** \( P \)-value in bold means statistically significant.

**Associations between *IL-11* gene polymorphisms and susceptibility of GC**

The genotype distributions of the enrolled polymorphisms of the *IL-11* gene are summarized in Table 2. All tested genotypes of each polymorphism in controls did not deviate from HWE \( (p>0.05) \). Among the six tagSNPs, we found that rs1126760 \( (C \text{ vs } T; \text{OR } =1.39, 95\% \text{ CIs } =1.13-1.70, P=0.002) \) and rs1126757 \( (C \text{ vs } T; \text{OR } =0.82, 95\% \text{ CIs } =0.72-0.93, P=0.002) \) were significantly associated with susceptibility of GC. Even adjusted for Bonferroni correction, the results were still significant \( (P=0.002\times6=0.012) \). For rs1126760, carriers of genotype TC \( (P<0.05) \) and CC \( (P<0.05) \) have a higher GC risk, compared with carriers of genotype TT. While for rs1126757, carriers of genotype CC \( (P<0.05) \) have a lower GC risk, compared with carriers of genotype TT. Results of the dominant and recessive model for rs1126760 and rs1126757 were also significant \( (P<0.05) \). However, we did not find any significant associations for rs1042505, rs7250912, rs4252556 and rs8104023 in any genetic models. For the positive results, FPRP was calculated (Table 3). Noteworthy findings were detected for 3 comparisons of rs1126760 \( (\text{TC vs TT, C vs T and dominant model}) \) and 2 comparisons of rs1126757 \( (\text{C vs T and dominant model}) \).

**Interaction analyses between *IL-11* gene polymorphisms and *H. pylori* infection**

In order to evaluate the effects of the gene–environmental interaction between *IL-11* polymorphisms and *H. pylori* infection on the susceptibility of GC, analyses of joint effects were performed for the two promising SNPs (Table 4). Significant interaction with *H. pylori* infection was identified for rs1126760 \( (P=0.005) \). We found 3.35-fold \( (95\% \text{ CIs } =2.69-4.18) \) elevated GC risk for subjects with genotype TC+CC and with *H. pylori* infection. We did not find any significant interaction for SNP rs1126757.

**Associations between *IL-11* gene polymorphisms and serum *IL-11* level, and mRNA expression correlation analysis of *IL-11***

As shown in Table 5, we analyzed the associations between *IL-11* gene polymorphisms and serum *IL-11* level in control. *IL-11* rs1126760 was significantly
Table 2 Genetic variants of the IL-11 gene and susceptibility of GC

| SNP          | Cases | Controls | Adjusted OR (95% CI)* | P-value |
|--------------|-------|----------|-----------------------|---------|
| rs1042505    |       |          |                       |         |
| GG           | 570   | 603      | 1.00 (reference)      |         |
| AG           | 275   | 269      | 1.12 (0.84–1.50)      | 0.428   |
| AA           | 31    | 25       | 1.36 (0.76–2.45)      | 0.300   |
| A vs G       | 306/294/603 | 1.15 (0.88–1.49) | 0.314 |
| Dominant     | 570   |          |                       |         |
| model        |       |          |                       |         |
| Recessive    | 31/25 | 133 (0.74–2.40) | 0.343 |
| rs1126760    |       |          |                       |         |
| TT           | 610   | 675      | 1.00 (reference)      |         |
| TC           | 248   | 214      | 1.33 (1.05–1.69)      | 0.016   |
| CC           | 21    | 9        | 2.69 (1.26–5.72)      | 0.010   |
| C vs T       | 269/223/675 | 1.39 (1.13–1.70) | 0.002 |
| Dominant     | 610   |          |                       |         |
| model        |       |          |                       |         |
| Recessive    | 21/9 | 2.51 (1.18–5.37) | 0.017 |
| model        | 858   |          |                       |         |
| rs1126760    |       |          |                       |         |
| TT           | 610   | 675      | 1.00 (reference)      |         |
| TC           | 248   | 214      | 1.33 (1.05–1.69)      | 0.016   |
| CC           | 21    | 9        | 2.69 (1.26–5.72)      | 0.010   |
| C vs T       | 269/223/675 | 1.39 (1.13–1.70) | 0.002 |
| Dominant     | 610   |          |                       |         |
| model        |       |          |                       |         |
| Recessive    | 21/9 | 2.51 (1.18–5.37) | 0.017 |
| model        | 858   |          |                       |         |
| rs7250912    |       |          |                       |         |
| CC           | 753   | 762      | 1.00 (reference)      |         |
| CG           | 113   | 124      | 0.96 (0.84–1.10)      | 0.543   |
| GG           | 8     | 9        | 0.94 (0.53–1.66)      | 0.820   |
| G vs C       | 121/133/762 | 0.96 (0.84–1.09) | 0.523 |
| Dominant     | 753   |          |                       |         |
| model        |       |          |                       |         |
| Recessive    | 8/766 | 9/886   | 0.95 (0.53–1.62)      | 0.838   |
| model        |       |          |                       |         |
| rs4252556    |       |          |                       |         |
| TT           | 681   | 711      | 1.00 (reference)      |         |
| TC           | 189   | 180      | 1.14 (0.83–1.56)      | 0.411   |
| CC           | 7     | 5        | 1.52 (0.46–5.07)      | 0.496   |
| C vs T       | 186/185/711 | 1.15 (0.85–1.55) | 0.360 |
| Dominant     | 681   |          |                       |         |
| model        |       |          |                       |         |
| Recessive    | 7/870 | 5/891   | 1.49 (0.44–5.01)      | 0.518   |
| model        |       |          |                       |         |
| rs8104023    |       |          |                       |         |
| TT           | 605   | 619      | 1.00 (reference)      |         |
| TC           | 235   | 234      | 1.07 (0.65–1.76)      | 0.793   |
| CC           | 33    | 31       | 1.13 (0.56–2.28)      | 0.727   |
| C vs T       | 265/265/619 | 1.08 (0.71–1.63) | 0.730 |
| Dominant     | 605   |          |                       |         |
| model        |       |          |                       |         |
| Recessive    | 33/31 | 1.12 (0.55–2.30) | 0.748 |
| model        | 840   |          |                       |         |

Table 2 (Continued).

| SNP          | Cases | Controls | Adjusted OR (95% CI)* | P-value |
|--------------|-------|----------|-----------------------|---------|
| rs1126757    |       |          |                       |         |
| TT           | 559   | 514      | 1.00 (reference)      |         |
| TC           | 278   | 313      | 0.85 (0.73–0.99)      | 0.038   |
| CC           | 40    | 61       | 0.63 (0.44–0.90)      | 0.012   |
| C vs T       | 318/374/514 | 0.81 (0.70–0.95) | 0.008 |
| Dominant     | 559   |          |                       |         |
| model        |       |          |                       |         |
| Recessive    | 40/61/827 | 0.67 (0.47–0.96) | 0.029 |
| model        | 837   |          |                       |         |

Notes: *Adjusted for age, gender, smoking and drinking status, HP infection, and education level. P-value in bold means statistically significant.

Expression of IL-11 gene with development and prognosis of GC

Figure 1 presents the association of expression of IL-11 gene with the development and prognosis of GC. The expression of the IL-11 gene in GC tissues was significantly higher than that in adjacent normal tissues (Figure 1A, P<0.001). We also found that the expression of the IL-11 gene was significantly associated with overall survival, first progression and post-progression survival of GC (Figure 1B–D, P<0.001).

Discussion

IL-11 functions as a hub of various carcinogenic pathways and plays an essential role in the carcinogenesis of GC. In the current study, we first explored the genetic associations of the IL-11 gene as well as its interaction with H. pylori infection in the development of GC in a Chinese population. We found that IL-11 rs1126760 was significantly associated with susceptibility of GC and higher serum and expression level of IL-11. Significant interaction with H. pylori infection was identified for rs1126760. Bioinformatics analyses revealed that the expression of IL-11 gene was significantly associated with the development and prognosis of GC.
IL-11 functions in many carcinogenic pathways of the cancers and acts as a function hub of many oncogenes. Since first described for its function and molecular structure by Kawashima et al.\textsuperscript{36} in 1992, many investigators have focused on its biological functions in carcinogenesis.\textsuperscript{13,20,21,37–40} IL-11 was considered as a potent anti-melanoma factor by Dams-Kozlowska.\textsuperscript{20} It could up-regulate the invasive and proliferative activity of human colorectal carcinoma cells.\textsuperscript{39} It was also a crucial cytokine promoting chronic gastric inflammation and associated tumorigenesis mediated by excessive activation of STAT3 and STAT1.\textsuperscript{20} The IL-6 family cytokine IL-11, more than a sidekick, has linked inflammation to cancer and may represent novel, therapeutic targets.\textsuperscript{13} IL-11 was involved in a variety of gastrointestinal malignancies and laid down a framework for its potential inhibition in many human cancers.\textsuperscript{40} Results in the current study also revealed that expression of IL-11 gene in tissues was

| SNP | OR (95% CI) | Statistical power | Prior probability |
|-----|-------------|--------------------|--------------------|
|     |             |                    | 0.25  | 0.1  | 0.01 | 0.001 | 0.0001 |
| rs1126760 |                   |                    | 0.066 | 0.174 | 0.699 | 0.959 | 0.996 |
| TC vs TT | 1.33 (1.05–1.69) | 0.837 | 0.320 | 0.586 | 0.940 | 0.994 | 0.999 |
| CC vs TT | 2.69 (1.26–5.72) | 0.065 | 0.043 | 0.118 | 0.595 | 0.937 | 0.993 |
| C vs T | 1.39 (1.13–1.70) | 0.722 | 0.016 | 0.047 | 0.350 | 0.844 | 0.982 |
| Dominant model | 1.39 (1.11–1.74) | 0.747 | 0.365 | 0.633 | 0.950 | 0.995 | 0.999 |
| Recessive model | 2.51 (1.18–5.37) | 0.092 |                    |        |        |        |        |

Note: *P*-value in bold means statistically significant.

| SNP | OR (95% CI) | Statistical power | Prior probability |
|-----|-------------|--------------------|--------------------|
|     |             |                    | 0.25  | 0.1  | 0.01 | 0.001 | 0.0001 |
| rs1126757 |                   |                    | 0.099 | 0.248 | 0.784 | 0.973 | 0.997 |
| TC vs TT | 0.85 (0.73–0.99) | 0.999 | 0.081 | 0.209 | 0.744 | 0.967 | 0.997 |
| CC vs TT | 0.63 (0.44–0.90) | 0.378 | 0.006 | 0.018 | 0.165 | 0.667 | 0.952 |
| C vs T | 0.82 (0.72–0.93) | 0.999 | 0.028 | 0.080 | 0.489 | 0.906 | 0.990 |
| Dominant model | 0.81 (0.70–0.95) | 0.992 | 0.146 | 0.339 | 0.849 | 0.983 | 0.998 |
| Recessive model | 0.67 (0.47–0.96) | 0.511 |                    |        |        |        |        |

Note: *P*-value in bold means statistically significant.

Table 4 Effects of interactions between HP infection and genetic variants of the IL-11 gene and susceptibility of GC

| Variants | HP infection | Case | Control | OR (95% CI) | Case | Control | OR (95% CI) |
|----------|--------------|------|---------|-------------|------|---------|-------------|
|          |              |      |         |             |      |         |             |
| rs1126760 | Negative     |      |         |             |      |         |             |
| TT       |              | 150  | 350     | 1.00 (reference) | 460  | 325     | 3.30 (2.61–4.17) |
| TC+CC    |              | 68   | 88      | 1.80 (1.25–2.60) | 201  | 135     | 3.35 (2.69–4.18) |

*P*-interaction=0.005

| rs1126757 | Negative     |      |         |             |      |         |             |
| TT       |              | 141  | 259     | 1.00 (reference) | 418  | 255     | 3.01 (2.34–3.88) |
| TC+CC    |              | 77   | 181     | 0.78 (0.56–1.09) | 244  | 205     | 2.64 (2.09–3.34) |

*P*-interaction=0.737

Table 5 Serum IL-11 levels in healthy controls

| SNP     | N (total N=100) | mean ± SD (pg/mL) | P-value |
|---------|-----------------|-------------------|---------|
| rs1126760 | TT              | 9.20±5.05         | <0.001  |
|         | TC              | 16.09±2.50        |         |
|         | CC              | 19.63±1.55        |         |
| rs1126757 | TT              | 13.48±5.70        | <0.001  |
|         | TC              | 8.93±3.40         |         |
|         | CC              | 4.33±1.56         |         |

Note: *P*-value in bold means statistically significant.

*IL*-11 functions in many carcinogenic pathways of the cancers and acts as a function hub of many oncogenes. Since first described for its function and molecular structure by Kawashima et al.\textsuperscript{36} in 1992, many investigators have focused on its biological functions in carcinogenesis.\textsuperscript{13,20,21,37–40} IL-11 was considered as a potent anti-melanoma factor by Dams-Kozlowska.\textsuperscript{20} It could up-regulate the invasive and proliferative activity of human colorectal carcinoma cells.\textsuperscript{39} It was also a crucial cytokine promoting chronic gastric inflammation and associated tumorigenesis mediated by excessive activation of STAT3 and STAT1.\textsuperscript{20} The IL-6 family cytokine *IL*-11, more than a sidekick, has linked inflammation to cancer and may represent novel, therapeutic targets.\textsuperscript{13} *IL*-11 was involved in a variety of gastrointestinal malignancies and laid down a framework for its potential inhibition in many human cancers.\textsuperscript{40} Results in the current study also revealed that expression of IL-11 gene in tissues was
significantly associated with development and prognosis of GC and provided strong evidence for the crucial role of \( IL-11 \) gene in the carcinogenesis process of GC.

In this study, \( IL-11 \) rs1126760 and rs1126757 were significantly associated with serum \( IL-11 \) level and susceptibility of GC. SNP rs1126760 (T/C) was located in the 3’ UTR region of the \( IL-11 \) gene, which would result in a target loss for hsa-miR-371a-5p.\(^{41}\) Kim et al\(^{26}\) found that rs1126760 was significantly associated with increased risk of Hirschsprung disease. Medrano et al\(^{42}\) reported its association with response to infliximab in Crohn’s disease. SNP rs1126757 (A82A) was located in the exon 3 of the \( IL-11 \) gene. Different from our results, Kim et al\(^{26}\) found that rs1126757 was significantly associated with increased risk.

Figure 1 Expression of \( IL-11 \) gene with development and prognosis of gastric cancer (GC). (A) The expression of the \( IL-11 \) gene in GC tissues (red) and adjacent normal tissues (black); (B) the expression of the \( IL-11 \) gene with overall survival of GC; (C) the expression of the \( IL-11 \) gene with first progression; (D) the expression of the \( IL-11 \) gene with post-progression survival.
of Hirschsprung disease. Differences in *IL-11* after treatment were found to be related to rs1126757. A CpG unit by rs1126757 interaction predictor of antidepressant response was also identified by Powell et al.44

Strength for this study included the following items. First, the large sample size ensured the enough statistical power for the finding of rs1126760 (93.8%). Second, interactions between the *IL-11* gene polymorphisms and *H. pylori* infection were evaluated on multiplicative scales, resulting in one significantly positive interaction for rs1126760. Several limitations should be addressed in this study, including the potential selection bias for case-control study and moderate sample size for interaction analyses.

Conclusively, our study provides strong evidence that genetic variants of the *IL-11* gene may interact with *H. pylori* infection and contributes to the development of GC. Our results increased the understanding of the possible mechanism of *IL-11* gene in the carcinogenesis and development of GC. Further studies with larger population and laboratory-based functional experiments are needed to validate our findings.

**Disclosure**

The authors report no conflicts of interest in this work.

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