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ORIGINAL RESEARCH

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]

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IL, 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.[12,13] Among them, *IL-11* drives gastric tumorigenesis independent of trans-signaling and acts as a hub of various carcinogenic pathways.[14–17] 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 Haploview 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 QIAamp 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 χ^2 test. Hardy–Weinberg equilibrium (HWE) was evaluated by Pearson's goodness-of-fit Chi-square (χ^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

	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			
Yes	320 (36.4%)	181 (20.1%)	**<0.001**
No	560 (63.6%)	719 (79.9%)	
HP infection			
Yes	662 (75.2%)	460 (51.1%)	**<0.001**
No	218 (24.8%)	440 (48.9%)	
Education level			
<High school	585 (66.5%)	395 (43.9%)	**<0.001**
≥High school	295 (33.5%)	505 (56.1%)	
Tumor site			
Cardia	285 (32.4%)		
Non-cardia	595 (67.6%)		
TNM stages			
I	131 (14.9%)		
II	157 (17.8%)		
III	407 (46.3%)		
IIV	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 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 ($P=0.002\times6=0.012$). For rs1126760, carriers of genotype TC (OR =1.33; 95%=1.05–1.69; $P=0.016$) and CC (OR =2.69; 95%=1.26–5.72; $P=0.010$) have a higher GC risk, compared with carriers of genotype TT. While for rs1126760, carriers of genotype TC (OR =0.85; 95%=0.73–0.99; $P=0.038$) and CC (OR =0.63; 95%=0.44–0.90; $P=0.012$) 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 (TC vs TT, C vs T and dominant model) and 2 comparisons of rs1126757 (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 for interaction =0.005). We found 3.35-fold (95% 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			1.15 (0.91–1.44)	0.242
Dominant model	306/570	294/603	1.15 (0.88–1.49)	0.314
Recessive model	31/845	25/872	1.33 (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			1.39 (1.13–1.70)	**0.002**
Dominant model	269/610	223/675	1.39 (1.11–1.74)	**0.004**
Recessive model	21/858	9/889	2.51 (1.18–5.37)	**0.017**
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			0.96 (0.85–1.08)	0.517
Dominant model	121/753	133/762	0.96 (0.84–1.09)	0.523
Recessive model	8/766	9/886	0.95 (0.55–1.62)	0.838
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			1.15 (0.87–1.52)	0.334
Dominant model	186/681	185/711	1.15 (0.85–1.55)	0.360
Recessive model	7/870	5/891	1.49 (0.44–5.01)	0.518
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			1.08 (0.76–1.54)	0.681
Dominant model	265/605	265/619	1.08 (0.71–1.63)	0.730
Recessive model	33/840	31/853	1.12 (0.55–2.30)	0.748
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			0.82 (0.72–0.93)	**0.002**
Dominant model	318/559	374/514	0.81 (0.70–0.95)	**0.008**
Recessive model	40/837	61/827	0.67 (0.47–0.96)	**0.029**

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

associated with higher serum *IL-11* level, while rs1126757 was significantly associated with lower serum *IL-11* level ($P<0.001$). In the mRNA expression correlation analysis of *IL-11*, we also found that minor allele of rs1126760 was associated with a higher expression level of *IL-11* in testis tissues (Figure 2).

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 and rs1126757 were 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.

Table 3 False-Positive Report Probability values for associations between genetic variants of the *IL-11* gene and susceptibility of GC

SNP	OR (95% CI)	Statistical power	Prior probability				
			0.25	0.1	0.01	0.001	0.0001
rs1126760							
TC vs TT	1.33 (1.05–1.69)	0.837	**0.066**	**0.174**	0.699	0.959	0.996
CC vs TT	2.69 (1.26–5.72)	0.065	0.320	0.586	0.940	0.994	0.999
C vs T	1.39 (1.13–1.70)	0.722	**0.043**	**0.118**	0.595	0.937	0.993
Dominant model	1.39 (1.11–1.74)	0.747	**0.016**	**0.047**	0.350	0.844	0.982
Recessive model	2.51 (1.18–5.37)	0.092	0.365	0.633	0.950	0.995	0.999
rs1126757							
TC vs TT	0.85 (0.73–0.99)	0.999	**0.099**	0.248	0.784	0.973	0.997
CC vs TT	0.63 (0.44–0.90)	0.378	**0.081**	0.209	0.744	0.967	0.997
C vs T	0.82 (0.72–0.93)	0.999	**0.006**	**0.018**	**0.165**	0.667	0.952
Dominant model	0.81 (0.70–0.95)	0.992	**0.028**	**0.080**	0.489	0.906	0.990
Recessive model	0.67 (0.47–0.96)	0.511	**0.146**	0.339	0.849	0.983	0.998

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					
	Negative			Positive		
	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)
rs1126760						
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						
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						

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[36] in 1992, many investigators have focused on its biological functions in carcinogenesis.[13,20,21,37–40] *IL-11* was considered as a potent anti-melanoma factor by Dams-Kozlowska.[20,37] It could up-regulate the invasive and proliferative activity of human colorectal carcinoma cells.[39] It was also a crucial cytokine promoting chronic gastric inflammation and associated tumorigenesis mediated by excessive activation of STAT3 and STAT1.[20] The IL-6 family cytokine *IL-11*, more than a sidekick, has linked inflammation to cancer and may represent novel, therapeutic targets.[13] *IL-11* was involved in a variety of gastrointestinal malignancies and laid down a framework for its potential inhibition in many human cancers.[40] Results in the current study also revealed that expression of *IL-11* gene in tissues was

Table 5 Serum IL-11 levels in healthy controls

SNP	N (total N=100)	mean ± SD (pg/mL)	*P*-value
rs1126760			<0.001
TT	73	9.20±5.05	
TC	23	16.09±2.50	
CC	4	19.63±1.55	
rs1126757			<0.001
TT	57	13.48±5.70	
TC	34	8.93±3.40	
CC	8	4.33±1.56	

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

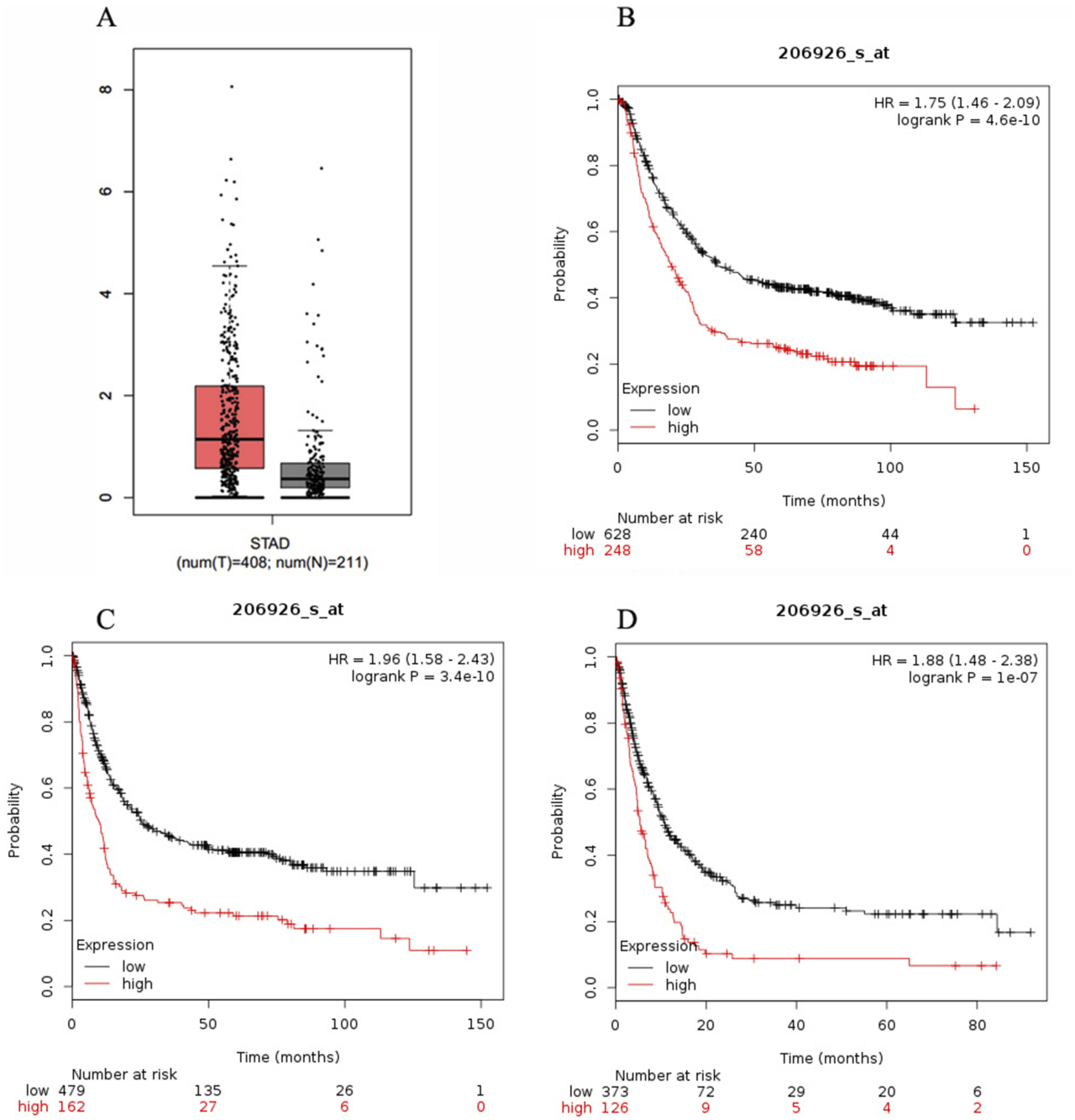

Figure 1 Expression of *IL-11* gene with development and prognosis of gastric cancer (GC). (**A**) The expression of the *IL-11* gene in GC tissues (red) and adjacent normal tissues (black); (**B**) the expression of the *IL-11* gene with overall survival of GC; (**C**) the expression of the *IL-11* gene with first progression; (**D**) the expression of the *IL-11* gene with post-progression survival.

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

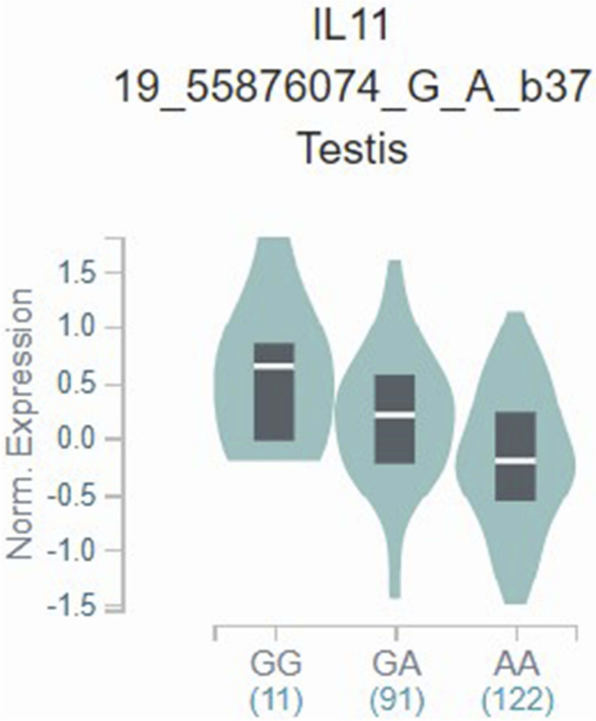

Figure 2 mRNA expression correlation analysis of *IL-11*.

of Hirschsprung disease. Differences in *IL-11* after treatment were found to be related to rs1126757.[43] 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.

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Disclosure

The authors report no conflicts of interest in this work.

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