Janus Kinase 2 Polymorphisms Are Associated with Risk in Patients with Gastric Cancer in a Chinese Population

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Abstract

**Aim:** To evaluate the impact of the Janus kinase 2 single nucleotide polymorphisms (SNPs) on gastric cancer risk.

**Methods:** In this hospital-based, case–control study, the genotypes were identified by polymerase chain reaction–restriction fragment length polymorphism protocols in 661 individuals (359 gastric cancer patients and 302 age and sex matched cancer-free controls).

**Results:** Both the frequency of A allele in rs2230724 and G allele in rs1887427 were more frequent in patients with gastric cancer ($P=0.013$ and $0.001$, respectively). Compared with the common genotype, subjects with the (AG+AA) genotypes of rs2230724 and the (AG+GG) genotypes of rs1887427 had a 59% and 98% increased risk of developing gastric cancer, respectively ($P=0.010$, adjusted OR = 1.59, 95% CI = 1.12–2.27; $P<0.001$, adjusted OR = 1.98, 95% CI = 1.39–2.81, respectively). Further stratified analysis showed that the association between the risk of gastric cancer and the rare genotypes of rs2230724 were more profound in the subgroups of elderly individuals ($>56$ years), males, nonsmokers and rural subjects, while the association between the risk and the rare genotypes of rs1887427 persisted in subgroups of younger individuals ($\leq56$ years), males, nonsmokers and both of rural and urban subjects.

**Conclusion:** The JAK2 gene rs2230724 and rs1887427 polymorphisms are associated with an increased risk of gastric cancer in a Chinese Han population.

Introduction

Gastric cancer remains the second leading cause of cancer-related mortality worldwide [1,2]. It is widely accepted that gastric carcinogenesis is a complex, multistep and multifactorial process involving genetic and epigenetic alteration of protein-coding protooncogenes and tumor-suppressor genes [3]. Genetic polymorphisms have been considered as the main genetic elements in the development of various diseases, including gastric cancer. Although the precise molecular mechanism remains unclear, genetic polymorphisms are thought to play important roles in gastric carcinogenesis [4]. Moreover, our previous epidemiologic studies also provided the evidence that the risk of gastric cancer was associated with genetic polymorphisms [5,6,7,8].

The Janus kinase 2 (JAK2) is a member of the family of tyrosine kinases (TKs) involved in cytokine receptor signaling. It is a key component of Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling [9]. It has been shown to participate in multifarious crucial biological responses related to diverse processes during embryogenesis, cell proliferation, cell survival and carcinogenesis [9,10,11,12]. The JAK/STAT pathway appears to be active in many solid tumors, including ovarian cancer, breast cancer, prostate cancer, lung cancer, gastric cancer as well as in hematologic malignancies [13,14,15,16,17,18]. In addition, JAK2/STAT3 pathway is closely associated with epithelial mesenchymal transition (EMT) and tumor metastasis in colon cancer and ovarian cancer [18,19]. Zhou et al. also found that the activation of JAK2 signaling pathway was likely to be associated with Helicobacter pylori-cytotoxin-associated protein A (CagA) induced high expression of gastrin in gastric cancer cells, which might be a main cause of stomach carcinogenesis [13]. Furthermore, it was reported that JAK2 was an oncogene and
down-regulating the expression of JAK2 could significantly suppress the proliferation of gastric cancer cells [20].

The gene for JAK2 is located on chromosomal region 9p24.1. To date, several JAK2 single nucleotide polymorphisms (SNPs) have been identified that they were significantly associated with polycythemia vera (PV) and essential thrombocythemia (ET), including rs7046736, rs10815146, rs12342421, rs10758669, rs3908850 and rs10574947 [21]. Recently, JAK2 SNP rs10758669 was also reported to be associated with increased susceptibility for Crohn’s disease (CD) [22,23]. It is reported that SNPs in the coding region could affect the gene expression, while variants located in the promoter region of a gene predominantly affect the transcriptional activity and then the gene expression [24]. Among the SNPs, rs2230724 is a coding exonic SNP and rs1887427 is an upstream promoter’s SNP, and their change might play a role in the transcriptional activity and expression of JAK2 gene.

However, the role of JAK mutations in solid tumors is emerging, and it has been proposed that mutations identified so far may just be the tip of the iceberg [25]. Recently, a study reported that the JAK2 V617F mutation led to constitutive signaling through the JAK2 TK, resulting in increased cellular proliferation and resistance to apoptosis in hematopoietic cells [26]. Given the importance and the potential biological mechanism of rs2230724 and rs1887427, we propose that the JAK2 polymorphisms may be contributed to the differences in susceptibility and severity of gastric cancer. In this work, a hospital-based case-control study was conducted to examine the association between the JAK2 polymorphisms and the risk of development or progression of gastric cancer in a Chinese Han population.

Materials and Methods

Ethics Statement

This study was conducted in Jiangsu Province in east of China. Before the research was conducted, ethical board approval from the First Affiliated Hospital of Nanjing Medical University was obtained, and all of the subjects provided written informed consent.

Subjects

This hospital-based case-control study comprised of 359 gastric cancer cases and 302 cancer-free controls. All cases were consecutively recruited at the First Affiliated Hospital of Nanjing Medical University in 2009 and 2010, and were diagnosed with gastric cancer based on histopathological evaluation. Those with secondary, recurrent tumors were excluded. All controls were randomly selected in the Department of General Surgery during the same period, without any history or diagnosis of malignancies and genetic disease. They were matched with the cases on age (±5 years) and sex. All of the subjects were unrelated Han nationality and from Jiangsu Province or its surrounding regions. The tumor histological grade was assessed according to World Health Organization criteria and was staged using the TNM staging of the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) system (2002). All sample data, including age, gender, weight, residence, hypertension, diabetes, smoke, tumor location, histological grade, depth of tumor invasion, lymph node metastasis and clinical stage were obtained by questionnaire or from the clinical and pathologic records. Individuals who formerly or currently smoked ≥10 cigarettes per day for at least 2 years were defined as smokers.

Genotyping

Genomic DNA was extracted from peripheral blood leukocytes by standard techniques. The protocol for genomic DNA extraction was described in our previous study [8]. A polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) assay was used to identify the JAK2 gene polymorphisms. The PCR was performed in a total volume of 20 μL reaction mixtures containing 2 μL 10× PCR buffer (MBI Fermentas), 1.75 mmol/L MgCl2, 0.15 mmol/L dNTP, 1 unit Taq polymerase (MBI fermentas), 150 ng genomic DNA and 0.25 μmol/L each primer (F-5’-TATTCTTATTTGCCCTGTATC-3’ and R-5’-CCTTGCAAGTGGTCTGTGA-3’ for rs2230724; F-5’-TGTTGGATGGAAAACCTAA-3’ and R-5’-AACCTTC-TACTCCCTGC/TTGG-5’ for rs1887427). For PCR amplification, after an initial denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 50°C for rs2230724 (34°C for rs1887427) for 30 s and elongation at 72°C for 60 s, with a final elongation at 72°C for 5 min.

For RFLP, The 267-bp and 261-bp PCR products of JAK2 polymorphisms (rs2230724 and rs1887427) were digested by the restriction enzyme BstNI and Bsu36I (New England BioLabs), 5 units for 16 h at 60°C and 37°C, respectively, followed by electrophoresis on a 3% agarose gel. For rs2230724, the common genotype homozygotes (GG) produced two bands at 183 and 84 bp, while the rare genotype homozygotes (AA) produced one band at 267 bp, and the heterozygous (AG) produced three bands at 267, 183 and 84 bp (Figure 1A). For rs1887427, the common genotype homozygotes (AA) produced one band at 261 bp, while the rare genotype homozygotes (GG) produced two bands at 151 and 110 bp and the heterozygous (AG) produced three bands at 261, 151 and 110 bp (Figure 1B).

Statistical Analysis

All the analyses were carried out with the SPSS 13.0 (SPSS Inc., Chicago, IL, USA) and were based on two-tailed probability. Differences were considered statistically significant at P<0.05. Quantitative variables departing from the normal distribution were summarized as median and analyzed by Mann-Whitney rank sum test. Pearson’s χ² test was used to test the difference in the distribution of categorical variables. The Hardy-Weinberg equilibrium of the JAK2 genotypes was evaluated by a goodness-of-fit χ² test. Odds ratio (OR) and 95% confidence interval (95% CI) were calculated to evaluate the association between the polymorphism and the risk of gastric cancer. The crude OR was assessed using the Woolf approximation method and the adjusted OR was computed by unconditional logistic regression method with adjustment for age, sex, smoking status, residence, hypertension and diabetes.

Results

Demographic Information

A total of 661 subjects (359 cases and 302 controls) were analyzed in this study. Demographic characteristics of the study participants were shown in Table 1. The age and gender were well matched in the case and control groups. Moreover, there was no significant difference in weight, smoking status, residence, history of hypertension, and diabetes between the case and control group.
Figure 1. Digestion of PCR products by restriction enzymes. (A) Genotypes of rs2230724, Lanes 1–3 and 8 AG heterozygous (267, 183 and 84 bp); lane 4 AA homozygotes (267 bp); lanes 5–7 GG homozygotes (183 and 84 bp). (B) Genotypes of rs1887427, lanes 14 and 16 GG homozygotes (151 and 110 bp); lanes 9–11 and 15 AA homozygotes (261 bp); lanes 12 and 13 AG heterozygous (261, 151 and 110 bp).

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Figure 2. Direct sequencing results for the JAK2 gene rs2230724 and rs1887427 polymorphisms. The polymorphisms were detected by RFLP and confirmed by direct PCR sequencing. The single base directed with a black arrowhead was the SNP site. (A), (B) and (C) Representatives of GG, AG, AA genotypes of rs2230724 by direct DNA sequencing, respectively. (D), (E) and (F) Representatives of AA, AG, GG genotypes of rs1887427 by direct DNA sequencing, respectively.

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For the polymorphisms of JAK2 (rs2230724 and rs1887427), the risks of carrying the rare genotypes were compared between the gastric cancer case and control groups, as shown in Table 2. There was no evidence for departure from Hardy-Weinberg equilibrium (HWE) in cases or controls ($P > 0.05$ for all).

To our data, there were significant differences of allele and genotype frequency between gastric cancer patients and cancer-free controls. As to the rs2230724, the A allele frequency was significantly higher in the case group (52.1%; $P = 0.013$, OR = 1.32, 95% CI = 1.06–1.64) than in the control group (45.2%). With the GG genotype as reference, the genotypes (AG+AA) were associated with an increased risk of gastric cancer ($P = 0.010$, adjusted OR = 1.59, 95% CI = 1.12–2.27) after adjustment for age, sex, smoking status, residence, hypertension, and diabetes. Moreover, the AG heterozygotes had a 52% increased risk of gastric cancer ($P = 0.030$, adjusted OR = 1.52, 95% CI = 1.04–2.21), and the AA homozygotes had a 79% increased risk ($P = 0.011$, adjusted OR = 1.79, 95% CI = 1.14–2.81).

Stratified Analysis of Polymorphism and Gastric Cancer Risk

As shown in Table 3, the results of stratified analyses by the median age of controls (56 years), sex, smoking status and residence with the JAK2 variant genotypes were performed. Considering the JAK2 polymorphism rs2230724, the increased risk of gastric cancer associated with the rare genotypes was significant in subjects ages >56 years ($P = 0.002$, adjusted OR = 2.25, 95% CI = 1.36–3.71), but not in subjects ages ≤56 years. In addition, the rare genotypes were associated with a 59% increased risk of gastric cancer in male subjects ($P = 0.036$, adjusted OR = 1.59, 95% CI = 1.03–2.45), whereas the association was not statistically significant in females subjects. Stratification by smoking status revealed a significant association of the polymor-
JAK2 Polymorphisms in Chinese Gastric Cancer

Recently, great advances were made in the understanding of the pathogenesis of the polymorphisms of JAK2 in patients with various diseases, including hematologic malignancies and Crohn’s disease [21, 22, 23, 29]. For example, rs2230724, a new SNP of JAK2, was associated with the susceptibility of acute leukemia and its subtypes. The A allele of rs2230724 was considered to be an important genetic determinant for acute leukemia and acute myeloid leukemia [29]. Moreover, Lee et al. [30] found that JAK2 SNP rs1887427 played major roles in prognosis and 13-cis-retinoic acid (13-c-RA) response in patients with head and neck cancer. Patients with all 3 wild genotypes (JAK2 rs1887427 and two other gene polymorphisms) had a 76% reduction in second primary

Table 3. Stratified analyses for variant JAK2 genotypes in cases and controls.

| Variable | (AG+AA)/GG for rs2230724 | Allelic odds ratios and 95% confidence intervals for rs2230724 | (AG+GG)/AA for rs1887427 | Allelic odds ratios and 95% confidence intervals for rs1887427 |
|----------|--------------------------|-----------------------------------------------------------|---------------------------|-----------------------------------------------------------|
|          | Cases, n (%) | Controls, n (%) | Adjusted OR (95% CI)* | P value | Cases, n (%) | Controls, n (%) | Adjusted OR (95% CI)* | P value |
| Age (y), median | | | | | | | | |
| ≤56 | 127(35.4)/37(10.3) | 118(39.1)/39(12.9) | 1.11 (0.66–1.87) | 0.693 | 76(21.2)/88(24.5) | 43(14.2)/114(37.7) | 2.43 (1.51–3.91) | <0.001 |
| >56 | 154(42.9)/41(11.4) | 93(30.8)/52(17.2) | 2.25 (1.36–3.71) | 0.002 | 54(15.0)/141(39.3) | 278(89)/118(39.1) | 1.60 (0.94–2.73) | 0.083 |
| Sex | | | | | | | | |
| Females | 88(24.5)/22(6.4) | 71(23.5)/29(9.6) | 1.69 (0.87–3.27) | 0.121 | 39(10.9)/71(23.5) | 26(8.6)/74(24.5) | 1.68 (0.91–3.12) | 0.099 |
| Males | 193(53.8)/56(15.6) | 140(46.4)/62(20.5) | 1.59 (1.03–2.45) | 0.036 | 91(25.3)/158(44.8) | 44(14.6)/158(52.3) | 2.18 (1.40–3.39) | 0.001 |
| Smoking Status | | | | | | | | |
| Smokers | 62(17.3)/23(6.4) | 46(15.2)/16(5.3) | 1.03 (0.47–2.26) | 0.948 | 24(6.7)/61(17.0) | 17(5.6)/45(14.9) | 1.15 (0.53–2.52) | 0.727 |
| Nonsmokers | 219(61.0)/55(15.3) | 165(54.6)/75(24.8) | 1.81 (1.21–2.72) | 0.004 | 106(29.5)/168(46.8) | 53(17.5)/187(61.9) | 2.37 (1.59–3.55) | <0.001 |
| Residence | | | | | | | | |
| Rural | 150(41.8)/48(13.4) | 116(38.4)/41(13.6) | 1.08 (0.66–1.77) | 0.752 | 73(20.3)/125(34.8) | 43(14.2)/114(37.7) | 1.64 (1.02–2.62) | 0.041 |
| Urban | 131(36.5)/30(8.4) | 95(31.5)/50(16.6) | 2.43 (1.42–4.17) | 0.001 | 57(15.9)/104(29.0) | 27(8.9)/118(39.1) | 2.68 (1.55–4.64) | <0.001 |

The bold in the table indicates statistically significant data.

*Adjusted for age, sex, smoking status, residence, hypertension, and diabetes.

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Discussion

JAK2 kinase is a member of the family of TKs involved in activation of several distinct intracellular signaling pathways. It is well known that JAK2 is a key component of Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling [9]. JAKs can also stimulate the activity of kinase PI3K (phosphatidylinositol-3-kinase) of the PI3K/Akt/mTOR pathway which inhibits apoptosis and stimulates cellular proliferation [9, 26]. Several epidemiologic studies have investigated the association between the dysfunction of JAK2 and a variety of human diseases, including cancer [9, 13, 14, 15, 16, 17, 18, 27]. Importantly, Pham et al. [20] showed that the activation of JAK/STAT pathway participated in the tumorigenesis of gastric cancer. Ding et al. [20] also reported that down-regulating the expression of JAK2 could significantly suppress the proliferation of gastric cancer cells. Therefore, JAK2 might be crucial for the coordinated proliferation, differentiation and tumorigenesis of gastric cancer.

In our current hospital-based case-control study, we detected the effect of JAK2 rs2230724 and rs1887427 gene polymorphisms on gastric cancer. Compared with the common genotype, subjects with the (AG+AA) genotypes of rs2230724 and the (AG+GG) genotypes of rs1887427 had a 59% and 90% increased risk of developing gastric cancer, respectively. Further stratified analysis showed that the association between the risk of gastric cancer and the rare genotypes of rs2230724 were more profound in the subgroups of elder individuals (≥56 years), males, nonsmokers and urban subjects, while the association between the risk and the rare genotypes of rs1887427 persisted in subgroups of younger individuals (≤56 years), males, nonsmokers and both of rural and urban subjects. According to our data, we for the first time found that the functional JAK2 polymorphisms conferred an increased risk of gastric cancer in a Chinese Han population.

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As the age and residence are potential confounding factors for susceptibility of gastric cancer, we adjusted the variable of age and residence in the subgroup analyses. However, the association in the subgroup of age and residence with gastric cancer risk is inconsistent. Stratified results revealed that risk associated with the rare genotypes of rs2230724 was more profound in the subgroups of elder individuals (>56 years) and urban subjects; that the risk associated with the rare genotypes of rs1887427 persisted in subgroups of younger individuals (≤56 years) and both subgroups of rural and urban subjects. Therefore, further studies with larger sample size are required to verify the association between the polymorphisms and gastric cancer progression.

Our study has several limitations. Firstly, the sample size was relatively small, which may have led to weak statistical significance. In this study, although the prevalence of AG genotype of rs2230724 was not significantly different (52.4% vs. 49.3%, respectively) in the cohorts of cases and negative cohort, the ratio of AG vs. GG (the reference) was significantly different (1.64 in controls), which was also indicated by the low P value (P=0.030) for the adjusted OR, suggesting an important role of JAK2 gene rs2230724 polymorphism in the risk of gastric cancer. Secondly, Helicobacter pylori is an independent risk factor for gastric cancer, but we did not explore the variable, because it was unethical to do the Helicobacter pylori test for every subject, especially for controls. Thirdly, in the subgroup analysis, we did not investigate the risk association with Lauren’s classification, alcoholic drinking status and so on. Because all cases were consecutively recruited at the First Affiliated Hospital of Nanjing Medical University between 2009 and 2010 and we did not collect the clinical data of Lauren’s classification, alcoholic drinking status et al. at that time. In our future study, we will definitely consider the related issues. Nevertheless, our results provided interesting information and valuable insights to future studies in this area.

### Table 4. Associations between variant JAK2 genotypes and clinicopathologic characteristics of gastric cancer.

| Variable          | (AG+AA) and GG for rs2230724 | Allelic odds ratios and 95% confidence intervals for rs2230724 | (AG+GG) and AA for rs1887427 | Allelic odds ratios and 95% confidence intervals for rs1887427 |
|-------------------|-----------------------------|-------------------------------------------------|-----------------------------|-------------------------------------------------|
| **Tumor Differentiation** |                          | Adjusted OR (95% CI)* P value                     | Adjusted OR (95% CI)* P value                     |                                                                 |
| Well              | AG+AA, N                   | 1.00                                            | AG+GG, N                   | 1.00                                            |
| Moderate          | 149                        | 5.04 (0.19–1.57)                                | 0.59                        | 1.37                                            |
| Poor              | 104                        | 0.83 (0.27–2.55)                                | 0.61                        | 0.69                                            |
| **Depth of Tumor Infiltration** |                          |                                                |                             |                                                 |
| T1                | 29                         | 1.00                                            | AG+AA, N                   | 1.00                                            |
| T2                | 29                         | 0.56 (0.16–1.91)                                | 0.35                        | 0.91                                            |
| T3                | 78                         | 0.59 (0.18–1.70)                                | 0.65                        | 0.52                                            |
| T4                | 145                        | 0.68 (0.24–1.96)                                | 0.72                        | 0.15                                            |
| **Lymph Node Metastasis** |                          |                                                |                             |                                                 |
| Negative          | 91                         | 1.00                                            | AG+AA, N                   | 1.00                                            |
| Positive          | 190                        | 0.64 (0.36–1.15)                                | 0.87                        | 0.35                                            |
| **Localization**  |                          |                                                |                             |                                                 |
| Cardia            | 88                         | 1.11 (0.65–1.92)                                | 0.69                        | 0.95                                            |
| Noncardia         | 193                        | 1.11 (0.65–1.92)                                | 0.69                        | 0.95                                            |

*Adjusted for age, sex, smoking status, residence, hypertension, and diabetes.*

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As the age and residence are potential confounding factors for susceptibility of gastric cancer, we adjusted the variable of age and residence in the subgroup analyses. However, the association in the subgroup of age and residence with gastric cancer risk is inconsistent. Stratified results revealed that risk associated with the rare genotypes of rs2230724 was more profound in the subgroups of elder individuals (>56 years) and urban subjects; that the risk associated with the rare genotypes of rs1887427 persisted in subgroups of younger individuals (≤56 years) and both subgroups of rural and urban subjects. Therefore, further studies with larger sample size are required to verify the association between the polymorphisms and gastric cancer progression.

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In conclusion, our study for the first time demonstrates that the JAK2 gene rs2230724 and rs1807427 polymorphisms are associated with an increased risk of gastric cancer in the Chinese Han population. Further studies with larger sample size and in different population are required to verify our initial observations.

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Author Contributions

Conceived and designed the experiments: LY DXL. Performed the experiments: DXL SL. Analyzed the data: DXL SL RHG ZHZ. Contributed reagents/materials/analysis tools: RHG ZHZ HX CY YZ. Wrote the paper: DXL SL LY.