Association between pepsinogen C gene polymorphism and genetic predisposition to gastric cancer

Hui-Jie Liu, Xiao-Lin Guo, Ming Dong, Lan Wang, Yuan Yuan

Hui-Jie Liu, Xiao-Lin Guo, Ming Dong, Lan Wang, Yuan Yuan, Cancer Institute, First Affiliated Hospital, China Medical University, Shenyang, 110001, Liaoning Province, China

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Correspondence to: Dr. Yuan Yuan, Cancer Institute, First Affiliated Hospital, China Medical University, 155 Northern Nanjing Street, Heping District, Shenyang 110001, Liaoning Province, China. yyuan@mail.cmu.edu.cn

Telephone: +86-24-22356666-6153 Fax: +86-24-22703576

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Abstract

AIM: To identify a molecular marker for gastric cancer, and to investigate the relationship between the polymorphism of pepsinogen C (PGC) gene and the genetic predisposition to gastric cancer.

METHODS: A total of 289 cases were involved in this study. 115 cases came from Shenyang area, a low risk area of gastric cancer, including 42 unrelated controls and 73 patients with gastric cancer. 174 cases came from Zhuanghe area, a high-risk area of gastric cancer, including 113 unrelated controls, and 61 cases from gastric cancer kindred families. The polymorphism of PGC gene was detected by polymerase chain reaction (PCR) and the relation between the genetic polymorphism of PGC and gastric cancer was examined.

RESULTS: Four alleles, 310bp (allele 1), 400bp (allele 2), 450bp (allele 3), and 480bp (allele 4) were detected by PCR. The frequency of allele 1 was higher in patients with gastric cancer than that in controls. Genotypes containing homogenous allele 1 were significantly more frequent in patients with gastric cancer than that in controls (0.33, 0.14, χ²=3.86, P<0.05). There was no significant difference between the control group of Zhanhe and the group of gastric cancer kindred. But the frequency of allele 1 was higher in control group of Zhanhe than that in control group of Shenyang and the group of gastric cancer kindred. The frequency of allele 1 was significantly higher in control group of Zhanhe area than those in control group of Shenyang area (0.33, 0.14, χ²=4.32, P<0.05). In the group of gastric cancer kindred the frequency of allele 1 was significantly higher than the control group of Zhanhe area (0.33, 0.14, χ²=4.47, P<0.05). Genotypes containing homogenous allele 1 were significantly more frequent in the group of gastric cancer kindred than those in control group of Shenyang area (0.36, 0.14, χ²=4.91, P<0.05).

CONCLUSION: These results suggest that there is some relation between pepsinogen C gene polymorphism and gastric cancer, and the person with homogenous allele 1 predisposes to gastric cancer than those with other genotypes. Pepsinogen C gene polymorphism may be used as a genetic marker for a genetic predisposition to gastric cancer. The distribution of pepsinogen C gene polymorphism in Zhanhe, a high-risk area of gastric cancer, is different from that in Shenyang, a low risk area of gastric cancer.

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INTRODUCTION

Gastric cancer is the second most common cancer in the world. Especially in China and other eastern Asian countries, the mortality of gastric cancer is still in the leading status of all cancers. The 5-year survival rate of gastric cancer is low, and identification and a better control of risk factors seem to be the most effective means of prevention. It was showed that many factors were ascribing to the cause of gastric cancer, including the living habit, nutrition[1-3], microbe[4-6], and genetic predisposition[7-10]. Recently, following the primary completion of Human Genome Project, the association of genetic polymorphisms with diseases came to the study frontier[11-14]. Genetic polymorphisms are defined as variations in DNA that are observed in 1 % or more of the population. The study of genetic polymorphisms promises to help define pathophysiologic mechanisms[15,16], to identify individuals at risk for disease[17-19] and to suggest novel targets for drug design and treatment[20-24].

Pepsinogen C (PGC), also known as progastricsin, is the precursor of pepsin C or gastricin. PGC can be detected throughout the stomach and proximal duodenum from the period of late infant stages to adult. Therefore it is also considered to be a mature marker of stomach cells[25]. PGC consists of two electrophoretic isozymogens[26]. No genetic variation was reported at the protein level. At the DNA level, however, an about 100bp insertion-deletion polymorphism was observed between exon 7 and exon 8 with several restriction enzymes. The polymorphism in PGC gene locus can be identified by both Southern blot and PCR methods.

In this study, we analyzed the PGC gene polymorphism of patients with gastric cancer and members with gastric cancer family history, and then examined the association between PGC gene polymorphism and gastric cancer.

MATERIALS AND METHODS

Patients

A total of 289 cases were involved in this study. 42 cases as health control came from the Blood Bank of the First Affiliated Hospital, China Medical University, whose health condition were checked up before blood was collected. 73 gastric cancer patients came from the Department of Oncology. 174 cases came from Zhanhe, an area with high gastric cancer mortality, in the eastern Liaoning Province, China as described previously[27], including 61 members from seven gastric cancer kindred families and 113 health controls whose family do not have gastric cancer history. In every gastric cancer kindred, at least two persons of the family are gastric cancer patients.
Analysis of PGC gene polymorphism

The genomic DNA from peripheral blood was amplified by PCR. The primers used were: upstream, 5’-AGCCCTAAGCTTGTCTGTG-3’; and the downstream, 5’-GGCCAGATCTGCGTTTGA-3’.[28] The reaction mixture including 32.15 pmol of each primer was subjected to 5 minutes at 95 °C; 35 cycles of one minute at 96 °C, one minute at 57 °C, one minute at 72 °C; with a final extension at 72 °C for 5 minutes. The amplification reaction proceeded in a thermocycler (PE-9 600). 12 μl of reaction mixture (50 μl in total volume) underwent electrophoresis in 2 % agarose gel, and the gel was stained with ethidium bromide.

Statistical analysis

The association between the polymorphism of PGC gene and gastric cancer was tested using \( \chi^2 \) test, with significance assigned to values below \( P<0.05 \).

RESULTS

Detection of PGC gene polymorphism

After PCR, four alleles with different size were obtained: 310bp (allele 1), 400bp (allele 2), 450bp (allele 3), and 480bp (allele 4) (Figure 1). These results showed a little difference from the data showed by Southern blot, which demonstrated two different alleles (3.5kb and 3.6kb). According to the study of Ohtaki et al., the 400bp, 450bp and 480bp of the PCR products correspond to the 3.6kb, and the 310bp correspond to 3.5bp of EcoRI fragments in Southern blot.[28]

Distribution of PGC gene polymorphism

Ten different genotypes were obtained from the four alleles. Table 1 showed the distribution of these ten genotypes of PGC gene polymorphism in gastric cancer patients, members of gastric cancer kindred, health controls of Shenyang and Zhuanghe areas. Table 2 showed an estimated frequency of the four alleles in the four groups, and Table 3 showed the distribution of allele 1 homogenotype in above four groups.

The frequency of allele 1 was higher in patients with gastric cancer than that in controls of Shenyang. Genotypes containing homogenous allele 1 were significantly more frequent in patients with gastric cancer than those in controls of Shenyang (\( P<0.05 \)). In the group of gastric cancer kindred the frequency of allele 1 was significantly higher than that in control group of Shenyang (\( P<0.05 \)). Genotypes containing homogenous allele 1 were significantly more frequent in the group of gastric cancer kindred than those in control group of Shenyang area (\( P<0.05 \)). The frequency of allele 1 was higher in control group of Zhuanghe area than that in control group of Shenyang area and genotypes containing homogenous allele 1 were significantly more frequent in the control group of Zhuanghe area than those in control group of Shenyang area (\( P<0.05 \)). There was no significant difference between the control group of Zhuanghe area and the group of gastric cancer kindred.

Table 1 The distribution of genotypes of PGC gene polymorphism in health control, gastric cancer patients, and gastric cancer kindred group

| Genotypes | Controls (Shenyang) | Gastric cancer patients | Controls (Zhuanghe) | Gastric cancer kindred |
|-----------|---------------------|-------------------------|--------------------|-----------------------|
| Alleles   |                     |                         |                    |                       |
| 1:1       | 6(0.14)             | 24(0.33)                | 37(0.33)           | 22(0.36)              |
| 1:2       | 10(0.24)            | 10(0.14)                | 9(0.08)            | 13(0.21)              |
| 1:3       | 7(0.17)             | 4(0.05)                 | 14(0.12)           | 4(0.07)               |
| 1:4       | 1(0.02)             | 1(0.01)                 | 9(0.08)            | 2(0.03)               |
| 2:2       | 4(0.10)             | 8(0.11)                 | 10(0.09)           | 7(0.11)               |
| 2:3       | 5(0.12)             | 8(0.11)                 | 9(0.08)            | 5(0.08)               |
| 2:4       | 1(0.02)             | 1(0.01)                 | 13(0.12)           | 1(0.16)               |
| 3:3       | 2(0.05)             | 10(0.14)                | 2(0.02)            | 3(0.05)               |
| 3:4       | 3(0.07)             | 5(0.07)                 | 8(0.07)            | 3(0.05)               |
| 4:4       | 3(0.07)             | 2(0.03)                 | 2(0.02)            | 1(0.16)               |
| Total     | 42                  | 73                      | 113                | 61                    |

\* \( P<0.05 \) vs compared with control group of Shenyang \( \chi^2=4.47 \).

Table 2 The frequency of four alleles of PGC gene polymorphism in health control, gastric cancer patients, and gastric cancer kindred group

| Alleles of PGC gene polymorphism | n (1/310bp) | n (2/400bp) | n (3/450bp) | n (4/480bp) |
|----------------------------------|-------------|-------------|-------------|-------------|
| Controls (Shenyang)              | 42          | 0.3571      | 0.2857      | 0.2262      | 0.1310      |
| Gastric cancer patients          | 73          | 0.4315      | 0.2397      | 0.2534      | 0.0753      |
| Controls (Zhuanghe)              | 113         | 0.4663      | 0.2389      | 0.1549      | 0.1504      |
| Gastric cancer kindred           | 61          | 0.5164\*    | 0.2705      | 0.1475      | 0.0656      |

\* \( P<0.05 \) vs compared with control group of Shenyang \( \chi^2=4.47 \).

Table 3 The distribution of allele 1 homogenotype in health control, gastric cancer patients, and gastric cancer kindred

| Alleles of PGC gene polymorphism | n (1/310bp) | others |
|----------------------------------|-------------|--------|
| Controls (Shenyang)              | 42          | 6(0.14) |
| Gastric cancer patients          | 73          | 24(0.33) |
| Controls (Zhuanghe)              | 113         | 37(0.33) |
| Gastric cancer kindred           | 61          | 22(0.36) |

\* \( P<0.05 \) vs compared with control group of Shenyang \( \chi^2=3.86 \); \( \chi^2=4.32 \); \( \chi^2=4.91 \).

DISCUSSION

Family members of gastric cancer patients have been found to have a 1.5-fold to 3-fold increase in the risk of developing this cancer.[29] This familial aggregation may be due to genetic or environmental factors shared by family members.[30-32] To understand the genetic predisposition to gastric cancer, we selected pepsinogen C gene as a marker gene, and focused first on the distribution of the PGC gene polymorphism in gastric cancer patient group and health control. After PCR,
four alleles of pepsinogen C gene with different size were obtained. The frequency of allele 1 was higher in patients with gastric cancer than that in controls. Genotypes containing homogenous allele 1 were significantly more frequent in patients with gastric cancer than those in controls. This result showed that there is relation between the pepsinogen C gene polymorphism and gastric cancer, and the person with homogenous allele 1 seems to predispose to gastric cancer than those with other genotypes.

To further study the relation of the PGC gene polymorphism to gastric cancer and the genetic background of Zhaunghe, the high-risk area of gastric cancer, we selected three groups as our next research objects: gastric cancer kindred group in Zhaunghe, the control group of Zhaunghe and the control group of Shenyang. There was no significant difference in the distribution of PGC gene polymorphism between the health control group of Zhaunghe and gastric cancer kindred group, though the frequency of allele 1 in gastric cancer kindred group was a little higher than that in the control group of Zhaunghe. Our understanding for this phenomenon was that the persons who lived in Zhaunghe did not move frequently because of the historical reason, and this consanguinity between the two groups was the main factor responsible for the above result. But the frequency of allele 1 was higher in control group of Zhaunghe area than that in control group of Shenyang area, and genotypes containing homogenous allele 1 were significantly more frequent in the control group of Zhaunghe area than those in control group of Shenyang area. The frequency of allele 1 in the group of gastric cancer kindred was also higher than that in controls. This result showed that the frequency of allele 1 in gastric cancer kindred group became lower in turn. The data in this study showed that the frequency of allele 1 and Genotype containing homogenous allele 1 were significantly more frequent in the group of gastric cancer kindred than that in the control group of Shenyang area. The result showed the distribution of PGC gene polymorphism in Shenyang area was different from that in Zhaunghe area.

The mortality of gastric cancer in Zhaunghe area is more than 50 per five hundred thousand. In the low risk area of that cancer, such as Shenyang, however, the mortality is less than 10 per five hundred thousand. From gastric cancer kindred group, the control groups of Zhaunghe and Shenyang, the risk ratio of gastric cancer becomes lower in turn. The data in this study showed that the frequency of allele 1 and Genotype containing homogenous allele 1 in the gastric cancer kindred group, the control groups of Zhaunghe and Shenyang in turn decreases, which is consistent with the risk ratio of gastric cancer in the above three groups. Therefore, we could conclude that the polymorphism of PGC gene may be related to the predisposition of gastric cancer, and the allele 1 associated with the risk of gastric cancer.

The mechanism of the association between PGC gene polymorphism and gastric cancer is not clear, in this study however, several hypotheses can be proposed. One is that the PGC gene itself is one of the genes responsible for gastric cancer. PGC, distributed throughout the stomach and proximal duodenum, is an important enzyme in stomach. It was reported that PGC not only was a digestive enzyme, but also might be a growth factor during the healing of gastric lesions[35] and the change of serum PGC was associated with many gastric diseases[34-37]. The polymorphism of PGC gene is in the intron between exon 7 and exon 8. Whether this polymorphism could affect the expression of PGC gene or regulate the PGC gene expression when the stomach was attacked by some pathogenetic factors was not known. In the following study, we will concentrate on the association of the PGC gene polymorphism and the PGC gene expression. It is interesting to note that in this study the frequency of allele 1 of PGC in the group of gastric cancer kindred was also higher than that in the group of gastric cancer group. As we know, the members of the gastric cancer kindred all come from Zhaunghe, a place in which the incidence of gastric cancer is higher, and so is that of some other gastric diseases. In the study of Ohtaki’s group, their data showed the polymorphism of PGC gene was associated with gastric body ulcer[26]. Comparing with our data, we can conclude the polymorphism of PGC is related to gastric lesions.

Another possible explanation of the association between the PGC gene polymorphism and gastric cancer was that the PGC gene was not itself responsible for the predisposition but one of the responsible genes was closely linked to it. It is interesting to note that the PGC gene was localized to human chromosome 6p21.1-pter by analysis of mouse x human somatic cell hybrids. The recent linkage analysis demonstrated that the PGC gene is 22cM proximal to HLA cluster which has been investigated to determine the associated with gastric disease[38-41], between D6S55 and D6S44, at a distance of 4.5 and 13.1cM. Further molecular biological studies using polymorphism markers for this chromosome region will clarify whether PGC polymorphism is linked to disequilibria of the causative genetic variations for gastric cancer. Lastly, the presence of reduced penetrance, other modifier genes, or an interaction with the environment may explain the association.

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