Risk of gastric cancer is associated with *PRKAA1* gene polymorphisms in Koreans

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**Abstract**

**AIM:** To evaluate the association between genetic polymorphisms of the gene encoding AMP-activated protein kinase (*PRKAA1*) and the risk of gastric cancer.

**METHODS:** The study subjects consisted of 477 age- and sex-matched case-control pairs. Genotyping was performed for 5 tag single nucleotide polymorphisms (SNPs): rs13361707, rs154268, rs3805486, rs6882903, and rs10074991. Associations between gastric cancer and putative risk factors (including the SNPs) were analyzed with multivariate conditional logistic regression models, after adjusting for potential confounding factors. Multiple testing corrections were implemented following methodology for controlling the false discovery rate. Gene-based association tests were performed by using the versatile gene-based association study (VEGAS) method.

**RESULTS:** In the dominant model, SNPs rs13361707 (odds ratio (OR) = 1.51, 95%CI: 1.07-2.11), rs154268 (OR = 1.65, 95%CI: 1.15-2.34), and rs10074991 (OR = 1.53, 95%CI: 1.09-2.16) were significantly associated with an increased risk of gastric cancer. In the recessive model, SNPs rs154268 (OR = 1.66, 95%CI: 1.22-2.22), rs6882903 (OR = 1.48, 95%CI: 1.09-2.00), and rs10074991 (OR = 1.47, 95%CI: 1.15-1.88) were significant risk or protective factors for gastric cancer. In the codominant model, the ORs of each of the 5 SNPs were statistically significant. All SNPs in the model showed a dose-response relationship between the minor allele frequency and the risk of gastric cancer. Most notably, subjects with a homozygous minor allele in SNP rs10074991 showed 2.15 times the risk of gastric cancer as subjects without a minor allele. The *PRKAA1* gene showed a significant gene-based association with gastric cancer in the VEGAS test.

**CONCLUSION:** All 5 tested tag SNPs of the *PRKAA1* gene (rs13361707, rs154268, rs3805486, rs6882903, and rs10074991) were significantly associated with gastric cancer.
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**Key words:** AMP-activated protein kinase; Gastric cancer; PRKAA1; Single nucleotide polymorphism; Case-control study

**Core tip:** There were a few studies to evaluate an association between PRKAA1 gene and gastric cancer. However, in previous study, only one single nucleotide polymorphism (SNP) (rs13361707) of PRKAA1 gene was focused. The purpose of this study was to evaluate the association between 5 SNPs of the gene encoding AMP-activated protein kinase (PRKAA1) and the risk of gastric cancer. All SNPs in the model showed a dose-response relationship between the minor allele frequency and the risk of gastric cancer. The PRKAA1 gene showed a significant gene-based association with gastric cancer in the versatile gene-based association study test.

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**INTRODUCTION**

Gastric cancer is the second most common cause of cancer-related mortality worldwide. Since the 1980s, South Korea, Japan, China, and other Asian countries have had a particularly high incidence of this disease, despite general trends of decreasing incidence and mortality.

A model of gastric carcinogenesis in humans has been derived based on evidence from various epidemiological and pathological studies. According to this model, gastric cancer arises in a sequence of stages: chronic gastritis, atrophic gastritis, intestinal metaplasia, and dysplasia. *Helicobacter pylori*, high salt intake, alcohol intake, smoking, diet, and genetic factors have been reported to be involved in gastric carcinogenesis.

AMP-activated protein kinase (AMPK) is an energy sensing/signaling intracellular protein, and a conserved serine/threonine kinase that regulates energy homeostasis and metabolic stress. AMPK is activated by phosphorylation when the AMP/ATP ratio is high. Activated AMPK switches on ATP-generating (catabolic) pathways and switches off ATP-consuming (anabolic) pathways. AMPK activation is known to inhibit the accumulation of lipid in the body, decrease the biosynthesis of fatty acids and cholesterol, and increase the oxidation of fatty acids.

Considerable evidence indicates that AMPK activation suppresses cell proliferation in both tumor and non-malignant cells. These results of AMPK activation are mediated through various mechanisms, including G1 phase arrest in the cell cycle, and the inhibition of fatty acid and protein synthesis. Regulation of the cell cycle by AMPK is mediated through activation of the p53-p21 axis pathway, activation of tumor suppressor LKB1, inhibition of the mammalian target of rapamycin pathway, and other similar mechanisms. Based on this evidence, research on AMPK function has focused on its important role in development, and on its potential use as a therapeutic target for some cancers. It is possible that AMPK plays an important role in gastric carcinogenesis and, therefore, polymorphic alleles of the encoding gene could modify individual susceptibility to gastric cancer. Recently, Song et al reported that the rs13361707 single nucleotide polymorphism (SNP) of the protein kinase, AMP-activated alpha 1 catalytic subunit (PRKAA1) gene was associated with an increased risk of gastric cancer in the Korean population. However, because their study only examined the rs13361707 SNP of the PRKAA1 gene, it remains important to elucidate the associations between other SNPs of PRKAA1 and gastric cancer.

Accordingly, the aim of the present study was to evaluate the associations between 5 polymorphic alleles of PRKAA1, the gene that encodes AMPK, and gastric carcinogenesis in Koreans.

**MATERIALS AND METHODS**

**Ethics**

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved by the institutional review boards of Chungbuk National University Hospital, South Korea (IRB No. 2011-09-071). All subjects had provided written informed consent.

**Study subjects**

The subjects included in this study consisted of 477 newly diagnosed gastric cancer patients and an equal number of age- (within 3 years) and sex-matched controls. The diagnoses of patients with gastric cancer were confirmed at Chungbuk National University Hospital and Eulji University Hospital, which are located in a geographically central region of the South Korea. Control subjects did not have a previous diagnosis of any type of cancer, and were selected from individuals who had received routine medical examinations at these hospitals. The case and control groups each included 301 men and 176 women. The mean ± SD age was 58.7 ± 9.9 years in the case group and 57.8 ± 10.2 years in the control group.

Trained interviewers interviewed all subjects by using a structured questionnaire, which included questions on demographic factors, smoking habits, alcohol consumption, and dietary habits. Peripheral blood and urine samples were collected from all the subjects.

**Selection of PRKAA1 SNPs**

We selected SNPs of PRKAA1 from several prominent
Table 1  Frequencies of PRKAA1 polymorphisms in cases and controls

| SNP     | Position | Genotype case/control | Case | Control |
|---------|----------|-----------------------|------|---------|
| rs6829303 | 40801619  | CC                    | AA   | 0.148   |
|         |          | 311/342               | 9/8  | 0.183   |
| rs10074991 | 40826308  | AA                    | AG   | 0.541   |
|         |          | 97/136                | GG   | 0.573   |
| rs13361707 | 40827641  | TT                    | TC   | 0.542   |
|         |          | 97/135                | CC   | 0.632   |
| rs154268  | 40831625  | TT                    | TC   | 0.239   |
|         |          | 267/311               | CC   | 0.020   |
| rs3805486  | 40831802  | TT                    | TC   | 0.224   |
|         |          | 283/233               | CC   | 0.474   |
|         |          | 170/199               | 21/40| 0.786   |

1FREQ: Allele frequency; 2P-value deviation from Hardy-Weinberg Equilibrium (HWE). SNP: Single nucleotide polymorphism.

online databases (GeneCards, HUGE navigator, NCBI; www.ncbi.nlm.nih.gov/SNP) because this gene may be related to diet risk factors for gastric carcinogenesis. To select tagging SNP, we identified functional elements from the Functional Elements SNPs Database, used the tagger pairwise method from the International HapMap Project, and finally selected SNPs with a minor allele frequency $\geq 0.05$ in JPT (Japanese in Tokyo, Japan) and CHB (Han Chinese in Beijing, China) samples. SNPs that significantly deviated from the Hardy-Weinberg equilibrium were discarded.

Genomic DNA was extracted from whole blood by using a QuickGene-810 nucleic acid isolation system (Fujifilm, Tokyo, Japan) and QuickGene DNA Whole Blood Kit S (Kurabo, Osaka, Japan), in accordance with the manufacturer's instructions. DNA was stored at 4°C until use. SNP genotyping was performed by using a GoldenGate Genotyping Assay with VeraCode technology (Illumina, San Diego, CA, United States). A custom GoldenGate assay was designed for the analysis of the selected SNPs in the PRKAA1 gene. Those SNPs were then assessed for suitability for the GoldenGate genotyping platform, and the analysis was carried out on the validated SNPs. The average call rate was 99.40%. Genotyping was carried out by Macrogen (Seoul, South Korea).

**Statistical analysis**

Testing for deviation from the Hardy-Weinberg equilibrium was performed for each SNP in both cases and controls by using Pearson's $\chi^2$ test. $D$ values were measured by using Lewontin's method for all combinations of biallelic loci, and linkage disequilibrium blocks were structured by using Haplovieview version 4.2 (Daly Lab at the Broad Institute Cambridge, MA, United States). Haplotype blocks were constructed and statistically compared between cases and controls by using SNP Analyzer version 2.0 (ISTEC, Goyang, South Korea). Haplotype blocks which frequency over 5% were selected for analysis.

Student's $t$-test was used to compare the values of continuous variables in the patient and control groups. Associations between gastric cancer and putative risk factors (including the SNPs) were estimated by using odds ratios (ORs) and their corresponding 95%CI, as derived from multivariate conditional logistic regression models, after adjusting for potential confounding factors such as age, sex, smoking history, alcohol intake amount, total calorie intake, and education level. Homozygous reference genotypes, heterozygous alleles, and homozygous risk alleles in each SNP were coded as 0, 1, and 2 in the codominant model; 0, 1, and 1 in the dominant model; and 0, 0, and 1 in the recessive model, respectively. Benjamini and Hochberg's methods for control of the false discovery rate (FDR) were used for multiple testing corrections[19]. Two-sided adjusted $P$ values < 0.05 were considered to be statistically significant. FDR $Q$ values were calculated separately for the SNPs and haplotypes based on those numbers.

Gene-based association tests were performed by using the versatile gene-based association study (VEGAS) method[20].

The study power calculations were performed by using the “case - control for discrete traits” mode in the Genetic Power Calculator created by Shaun Purcell (http://pngu.mgh.harvard.edu/~purcell/gpc/ec2.html). The following parameters were applied: a risk allele frequency of 0.4, an alpha error of 0.01, and a disease prevalence of 0.1%. The power of a codominant model was 0.7768 when the heterozygous odds ratio was set to 1.5. The power of a dominant model was 0.8821 when the odds ratio for a genotype with 1 or 2 risk allele(s) was taken to be 2. The power of a recessive model was 0.8182 when a value of 2 was input for the odds ratio for a genotype with 2 risk allele(s). SAS version 9.2 (SAS Institute, Cary, NC) was used for all statistical analyses.

**RESULTS**

We explored the associations between 5 DNA polymorphisms in the PRKAA1 gene, which encodes AMPK, and gastric cancer risk. A total of 954 subjects were included in the analysis, comprising 477 gastric cancer cases and equal number of matched controls. There were no significant differences between the two groups in terms of age, gender, smoking status, or alcohol intake.
Table 2  Association between PRKAA1 polymorphisms and gastric cancer

| SNP       | OR (95%CI) Dominant model | \(P\) value | \(Q^2\) | OR (95%CI) Recessive model | \(P\) value | \(Q^2\) |
|-----------|---------------------------|-------------|---------|----------------------------|-------------|---------|
| rs6882903 | 1.48 (1.09-2.00)          | 0.0121      | 0.0230  | 1.21 (0.60-2.46)           | 0.5906      | 0.7583  |
| rs10074991| 1.53 (1.09-2.16)          | 0.0139      | 0.0230  | 1.47 (1.15-1.88)           | 0.0021      | 0.0045  |
| rs13361707| 1.57 (1.07-2.11)          | 0.0184      | 0.0230  | 1.13 (0.43-2.92)           | 0.8085      | 0.8885  |
| rs154268  | 1.65 (1.22-2.22)          | 0.0012      | 0.0060  | 1.66 (1.22-2.26)           | 0.0012      | 0.0045  |
| rs3805486 | 0.61 (0.34-1.09)          | 0.0916      | 0.0916  | 0.63 (0.46-0.85)           | 0.0027      | 0.0045  |

Reference alleles of each single nucleotide polymorphism (SNP) in logistic analysis are as follows; CC for rs6882903, AA for rs10074991, and TT for rs13361707, rs154268 and rs3805486. \(\text{P}\) values for logistic analysis of two alternative models (dominant and recessive) adjusted with calorie intake, smoking history, alcohol intake and educational level; \(Q\) False discovery rate Q value.

Table 3  Codominant model odds ratios of the PRKAA1 polymorphisms for gastric cancer

| SNPs      | Adjusted OR (95%CI) | \(P\) value | \(Q^2\) |
|-----------|---------------------|-------------|---------|
| rs6882903 | CC      | 1.00        | 0.0123  | 0.0123 |
|           | CA      | 1.46 (1.07-2.00) | 0.128  |
|           | AA      | 1.75 (1.06-3.00) | 0.062  |
| rs10074991| AA      | 1.00        | 0.0005  | 0.0023 |
|           | AG      | 1.30 (0.90-1.87) | 0.329  |
|           | GG      | 2.15 (1.40-3.30) | 0.051  |
| rs13361707| TC      | 1.29 (0.90-1.85) | 0.123  |
|           | CC      | 2.05 (1.35-3.14) | 0.024  |
| rs154268  | TT      | 1.00        | 0.0017  | 0.0028 |
|           | TC      | 1.63 (1.20-2.22) | 0.084  |
|           | CC      | 1.77 (0.82-3.83) | 0.201  |
| rs3805486 | TT      | 1.00        | 0.0009  | 0.0123 |
|           | TC      | 0.72 (0.40-1.32) | 0.345  |
|           | CC      | 0.54 (0.20-0.49) | 0.006  |
| VEGAS statistics (\(P\)) | 46.0927 | 0.0004 |

\(\text{P}\) values for logistic analysis of codominant model adjusted with age, sex, calorie intake, smoking history, alcohol intake and educational level; \(Q\) False discovery rate Q value. SNP: Single nucleotide polymorphism; VEGAS: Versatile gene-based association study.

Table 1 presents the frequencies of the 5 selected SNPs in the study subjects. The genotype distributions at all 5 SNPs were in Hardy-Weinberg equilibrium, with non-significant \(\chi^2\) values.

Haplotype linkage disequilibrium block and haplotype frequencies for PRKAA1 are presented in Figure 1. Common haplotypes (frequency > 5%) of the block were found in 93.6% of cases, and 95.7% of controls.

The frequencies and distribution of genotypes are presented in Tables 2 and 3, which also report the odds ratios for the associations between each polymorphism and gastric cancer. We performed the PRKAA1 gene association analysis with dominant, recessive, and codominant models by using conditional logistic regression. In the dominant model, 4 of 5 SNPs we observed were significantly associated with an increased risk of gastric cancer. SNPs rs13361707 (“C” allele, OR = 1.51, 95%CI: 1.07-2.11, \(P = 0.018\), FDR \(Q = 0.023\)), rs154268 (“C” allele, OR = 1.65, 95%CI: 1.22-2.22, \(P = 0.001\), FDR \(Q = 0.006\)), rs6882903 (“A” allele, OR = 1.48, 95%CI: 1.09-2.00, \(P = 0.012\), FDR \(Q = 0.023\)), and rs10074991 (“G” allele, OR = 1.53, 95%CI: 1.09-2.16, \(P = 0.014\), FDR \(Q = 0.023\)) were significantly associated with an increased risk of gastric cancer. In the recessive model, SNP rs154268 (OR = 1.66, 95%CI: 1.22-2.26, \(P = 0.023\)) was significantly associated with an increased risk of gastric cancer.
Table 4 Association between PRKAA1 haplotypes and gastric cancer

| Haplotypes | Codominant | Dominant | Recessive |
|------------|------------|----------|-----------|
|            | OR (95%CI) | P value  | Q²        | OR (95%CI) | P value  | Q²        | OR (95%CI) | P value  | Q²        |
| PRKAA1     |            |          |           |            |          |           |            |          |           |
| haplotype  |            |          |           |            |          |           |            |          |           |
| block 1    |            |          |           |            |          |           |            |          |           |
|            | 1.57 (0.93-2.65) | 0.205   | 0.980     | 1.18 (0.92-1.53) | 0.195   | 0.980     | 1.48 (0.89-2.47) | 0.126   | 1.000    |
|            | 0.79 (0.46-1.36) | 0.574   | 0.980     | 1.02 (0.79-1.32) | 0.895   | 0.980     | 0.77 (0.45-1.32) | 0.339   | 1.000    |
|            | 0.44 (0.25-0.77) | 0.002   | 0.062     | 0.67 (0.52-0.87) | 0.002   | 0.063     | 0.50 (0.29-0.87) | 0.012   | 0.346    |
|            | 1.44 (0.53-3.90) | 0.032   | 0.456     | 1.45 (1.10-1.92) | 0.009   | 0.124     | 1.29 (0.48-3.50) | 0.614   | 1.000    |

1P values for logistic analysis of three alternative models (codominant, dominant and recessive), the P values for haplotype association were calculated by the single nucleotide polymorphism Analyzer™ 2.0 software; False discovery rate Q value.

0.001, FDR $Q = 0.005$), rs3805486 (OR = 0.63, 95%CI: 0.46-0.85, $P = 0.003$, FDR $Q = 0.005$) and rs10074991 (OR = 1.47, 95%CI: 1.15-1.88, $P = 0.002$, FDR $Q = 0.005$) were significant risk factors for gastric cancer (Table 2). In the codominant model, the odds ratios were statistically significant for all 5 SNPs. All SNPs in the model showed dose-response relationships between minor allele frequency and the risk of gastric cancer. Most notably, subjects with a homozygous minor allele in SNP rs10074991 showed 2.15 times of risk for gastric cancer, compared with subjects who did not have a minor allele (Table 3).

To evaluate the association between gastric cancer and all SNPs within the PRKAA1 gene (rather than each SNP individually) we performed a gene-based analysis following the VEGAS method, the results of which indicated that SNPs in PRKAA1 had a statistically significant association with gastric cancer in all 3 models ($P = 0.0054$, 0.0001, and 0.0004 for the dominant, recessive, and codominant models, respectively).

The haplotype block was also evaluated for an association with the risk of gastric cancer (Table 4), but none of the results were significant in each of the 3 models.

**DISCUSSION**

In this study, we hypothesized that genetic polymorphisms in PRKAA1 might contribute to gastric cancer development by affecting the regulation of energy metabolism. Activated AMPK inactivates a number of metabolic enzymes involved in ATP-consuming cellular events (such as fatty acid, cholesterol, and protein synthesis) and also activates ATP-generating processes (such as the uptake and oxidation of glucose and fatty acids)\[^{12,13}\]. Besides energy metabolism, AMPK also functions as a suppressor of cell proliferation\[^{14}\]. Consequently, some research on AMPK has focused on its potential role as a therapeutic target for cancer.

A recent genome-wide association study identified a new SNP (rs13361707) in the PRKAA1 gene that is significantly associated with increased susceptibility to gastric cancer\[^{21,22}\]. Additionally, Song et al\[^{18}\] reported that the rs13361707 SNP was associated with an increased risk of gastric cancer in the Korean population. In their replication study, rs13361707 TC and CC genotypes were associated with a significantly increased risk of gastric cancer (OR = 1.29 for TC vs TT, OR = 1.68 for CC vs TT). In agreement with these findings, our result also showed that the rs13361707 SNP is associated with gastric cancer (OR = 1.29 for TC vs TT, OR = 2.05 for CC vs TT). Together, these results suggest that rs13361707 SNP might play an important role in the development of gastric cancer. However, since rs13361707 is not the only SNPs found in this gene, it remained important to examine associations between other SNPs of PRKAA1 and gastric cancer development.

In the present study, we evaluated the associations of 5 SNPs of PRKAA1 gene with gastric cancer. Interestingly, we found that all 5 of the tested SNPs of PRKAA1 we tested were associated with a significantly increased risk of gastric cancer. Most notably, subjects with a homozygous minor allele in SNP rs10074991 were at 2.15 times the risk of gastric cancer, compared with subjects who did not have a minor allele. After controlling the FDR, the associations of these SNPs remained statistically significant in the codominant model. In a gene-based association test, the PRKAA1 gene was found to be significantly associated with gastric cancer. These results suggest that genetic polymorphism of PRKAA1 might play an important role in gastric carcinogenesis.

Although the biological mechanism underlying the association between PRKAA1 and gastric cancer has not been clarified, these significant associations could potentially be explained by the ability of activated AMPK phosphorylates p53 to induce G1/S arrest. Further, the AMPK-p53 connection may represent a cell cycle checkpoint\[^{23}\]. Therefore, individuals with mutant PRKAA1 alleles, which encode inactive AMPK, may be vulnerable to gastric cancer. Anti-inflammatory action by AMPK could provide another explanation of the association between SNPs of PRKAA1 and gastric cancer.

A recent study has reported that activated AMPK can counter-regulate macrophage inflammatory function\[^{24}\] and activate some anti-inflammatory agents\[^{25}\]. Loss of anti-inflammatory action by AMPK in the body of individuals with mutant PRKAA1 alleles results in more severe injury of the epithelium\[^{26}\]. Bone marrow-derived cells are recruited at these sites of epithelial damage, and these cells can be a potential source of malignancy\[^{27}\]. To our knowledge, there is no study addressed association between PRKAA1 gene and gastric cancer except in Chinese and Korean population. Since SNPs frequency are different according to the population, it is need to
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