

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

Yong-Dae Kim, Dong-Hyuk Yim, Sang-Yong Eom, Sun In Moon, Hyo-Yung Yun, Young-Jin Song, Sei-Jin Youn, Taisun Hyun, Joo-Seung Park, Byung Sik Kim, Jong-Young Lee, Hee Kwan Won, Heon Kim

Yong-Dae Kim, Dong-Hyuk Yim, Sang-Yong Eom, Sun In Moon, Heon Kim, Department of Preventive Medicine, College of Medicine, Chungbuk National University, Cheongju 361-763, South Korea

Hyo-Yung Yun, Young-Jin Song, Department of Surgery, College of Medicine, Chungbuk National University, Cheongju 361-763, South Korea

Sei-Jin Youn, Department of Internal Medicine, College of Medicine, Chungbuk National University, Cheongju 361-763, South Korea

Taisun Hyun, Department of Food and Nutrition, Chungbuk National University, Cheongju 361-763, South Korea

Joo-Seung Park, Department of Surgery, College of Medicine, Eulji University, Daejeon 301-832, South Korea

Byung Sik Kim, Department of Surgery, Asan Medical Center, College of Medicine, Ulsan University, Seoul 138-736, South Korea

Jong-Young Lee, Center for Genome Science, National Institute of Health, Cheongju 363-951, South Korea

Hee Kwan Won, Department of Internal Medicine, Division of Endocrinology and Metabolism, School of Medicine, Konyang University, Daejeon 302-718, South Korea

Author contributions: Kim YD, Lee JY, and Kim H designed the study protocol; Yim DH, Eom SY, and Moon SI performed the statistical analysis and data interpretation; Song YJ, Yun HY, Park JS, Youn SJ, Kim BS, Won HK and Hyun T contributed equally to this study through the selection of subjects, sampling, and clinical data acquisition; Kim YD and Kim H drafted the manuscript.

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Correspondence to: Heon Kim, Professor, Department of Preventive Medicine and Medical Research Institute, College of Medicine, Chungbuk National University, 52 Naesudong-ro, Hungdok-gu, Cheongju 361-763, South Korea. kimheon@cbu.ac.kr
Telephone: +82-43-2612864 Fax: +82-43-2742965

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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: 1.22-2.22), *rs6882903* (OR = 1.48, 95%CI: 1.09-2.00), 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: 1.22-2.26), *rs3805486* (OR = 0.63, 95%CI: 0.46-0.85), 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 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^[1]. 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^[2,3].

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^[4]. *Helicobacter pylori*, high salt intake, alcohol intake, smoking, diet, and genetic factors have been reported to be involved in gastric carcinogenesis^[5-9].

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^[10]. AMPK is activated by phosphorylation when the AMP/ATP ratio is high^[11]. Activated AMPK switches on ATP-generating (catabolic) pathways and switches off ATP-consuming (anabolic) pathways^[12,13]. 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^[12].

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^[14], and the inhibition of fatty acid and protein synthesis^[13,15]. 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^[16]. 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^[16,17]. 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.*^[18] 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 \pm 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				Freq ¹	HWE ²	Freq ¹	HWE ²
rs6882903	40801619	CC	CA	AA	N	0.183	0.034	0.148	0.371
		311/342	156/125	9/8	476/475				
rs10074991	40826308	AA	AG	GG	N	0.541	0.573	0.456	0.412
		97/136	242/244	136/94	475/474				
rs13361707	40827641	TT	TC	CC	N	0.542	0.632	0.459	0.510
		97/135	241/242	137/96	475/473				
rs154268	40831625	TT	TC	CC	N	0.239	0.020	0.188	0.576
		267/311	192/149	18/15	477/475				
rs3805486	40831802	TT	TC	CC	N	0.224	0.474	0.296	0.786
		283/233	170/199	21/40	474/472				

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

online databases (GeneCards, HUGO 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 ≥ 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 χ^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 Haploview 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. Benjaminin 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/cc2.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.

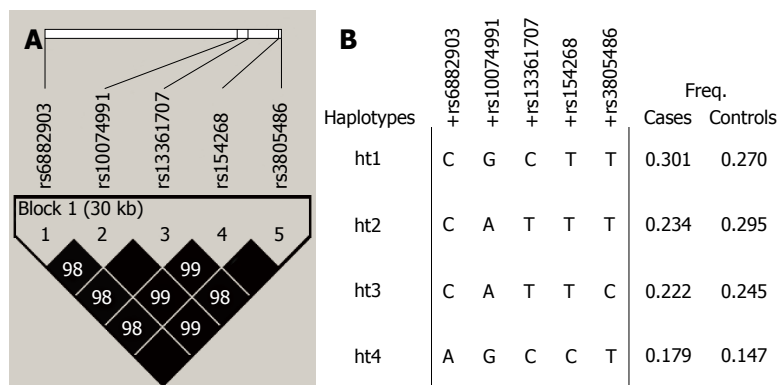


Figure 1 Haplotype linkage disequilibrium blocks and haplotype frequencies for *PRKAA1*. A: Linkage disequilibrium blocks and correlation coefficients among *PRKAA1* polymorphisms. Black squares indicate statistically significant allelic association between the pair of single nucleotide polymorphisms (SNPs), as measured by using the *D* statistic; darker gray indicate higher values of *D*, up to a maximum of 1; B: Haplotype frequencies of *PRKAA1* polymorphisms in the case and control groups. Freq: Allele frequency.

SNP	Dominant model			Recessive model		
	OR (95%CI)	<i>P</i> value ¹	<i>Q</i> ²	OR (95%CI)	<i>P</i> value ¹	<i>Q</i> ²
<i>rs6882903</i>	1.48 (1.09-2.00)	0.0121	0.0230	1.21 (0.60-2.46)	0.5906	0.7383
<i>rs10074991</i>	1.53 (1.09-2.16)	0.0139	0.0230	1.47 (1.15-1.88)	0.0021	0.0045
<i>rs13361707</i>	1.51 (1.07-2.11)	0.0184	0.0230	1.13 (0.43-2.92)	0.8085	0.8085
<i>rs154268</i>	1.65 (1.22-2.22)	0.0012	0.0060	1.66 (1.22-2.26)	0.0012	0.0045
<i>rs3805486</i>	0.61 (0.34-1.09)	0.0916	0.0916	0.63 (0.46-0.85)	0.0027	0.0045
VEGAS statistics (<i>P</i>)	30.0356 (0.0054)			56.0515 (0.0001)		

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*. ¹*P* values for logistic analysis of two alternative models (dominant and recessive) adjusted with calorie intake, smoking history, alcohol intake and educational level; ²False discovery rate *Q* value.

SNPs	Adjusted OR (95%CI)	<i>P</i> value ¹	<i>Q</i> ²
<i>rs6882903</i>	CC	1.00	0.0123
	CA	1.46 (1.07-2.00)	0.0123
	AA	1.75 (0.60-5.08)	0.0123
<i>rs10074991</i>	AA	1.00	0.0005
	AG	1.30 (0.90-1.87)	0.0005
	GG	2.15 (1.40-3.30)	0.0005
<i>rs13361707</i>	TT	1.00	0.0009
	TC	1.29 (0.90-1.85)	0.0009
	CC	2.05 (1.35-3.14)	0.0009
<i>rs154268</i>	TT	1.00	0.0017
	TC	1.63 (1.20-2.22)	0.0017
	CC	1.77 (0.82-3.83)	0.0017
<i>rs3805486</i>	TT	1.00	0.0099
	TC	0.72 (0.40-1.32)	0.0099
	CC	0.54 (0.30-0.98)	0.0099
VEGAS statistics (<i>P</i>)	46.0927 (0.0004)		

¹*P* values for logistic analysis of codominant model adjusted with age, sex, calorie intake, smoking history, alcohol intake and educational level; ²False discovery rate *Q* value. SNP: Single nucleotide polymorphism; VEGAS: Versatile gene-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 χ^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* =

Table 4 Association between *PRKAA1* haplotypes and gastric cancer

Haplotypes		Codominant			Dominant			Recessive		
		OR (95%CI)	P value ¹	Q ²	OR (95%CI)	P value ¹	Q ²	OR (95%CI)	P value ¹	Q ²
<i>PRKAA1</i>	CGCTT	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
haplotype	CATTT	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
block 1	CATTC	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
	CGCCT	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; ²False 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

further study in different races other than Asian.

The present study has several limitations. First, a relatively small number of patients and controls were enrolled in this study. Second, we could not obtain detailed data on the histological tumor types for the cases of gastric cancer. Finally, because the data of environmental factor for gastric cancer such as *H. pylori* infection and diet was not available in this study, we could not evaluate the gene-environmental interaction. It is needed further study about it.

In summary, the *PRKAA1* gene and 5 of its SNPs (*rs13361707*, *rs154268*, *rs3805486*, *rs6882903*, and *rs10074991*) were associated with an increased risk of gastric cancer in Koreans.

COMMENTS

Background

Gastric cancer is the second most common cause of cancer-related mortality worldwide. 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. It is known that AMPK activation suppresses cell proliferation in both tumor and non-malignant cells. Therefore, it is possible that AMPK plays an important role in gastric carcinogenesis and polymorphic alleles of the encoding gene could modify individual susceptibility to gastric cancer. 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.

Research frontiers

In the present study, the authors evaluated the associations of 5 single nucleotide polymorphisms (SNPs) of *PRKAA1* gene with gastric cancer. To our knowledge, this is the first replication study to indicate an association between *rs154268*, *rs3805486*, *rs6882903*, and *rs10074991* and gastric cancer development. Interestingly, all 5 SNPs of *PRKAA1* tested SNP 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.

Innovations and breakthroughs

There were a few studies to evaluate association between *PRKAA1* gene and gastric cancer. However, in previous study, only one SNP (*rs13361707*) of *PRKAA1* gene was focused. In this study, authors evaluated 5 SNPs of *PRKAA1* gene including *rs13361707* in associated with gastric cancer risk.

Applications

The result of this study showed that *PRKAA1* gene and its 5 SNPs (*rs13361707*, *rs154268*, *rs3805486*, *rs6882903*, and *rs10074991*) were associated with an increased risk of gastric cancer in Koreans. Further studies are needed to determine the mechanism which by *PRKAA1* and other environmental factors interact and influence the development of gastric cancer.

Peer review

This is a nice paper with a good summary of the issue and a well described methodology for studying 5 polymorphic alleles of *PRKAA1*, the gene that encodes AMPK, and gastric cancer in Koreans. In this study, the authors test the association between 5 SNPs of *PRKAA1* gene and gastric cancer in a Korean population. The *PRKAA1* gene has been implicated in carcinogenesis at several levels and the authors provide a reasonable rationale for this selection. The SNPs show nominally significant association to gastric cancer.

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