Int J Clin Exp Med 2015;8(7):11484-11489
www.ijcem.com /ISSN:1940-5901/IJCEM0010539

Original Article

Association between polymorphisms in *APE1* and *XRCC1* and the risk of gastric cancer in Korean population

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Received May 22, 2015; Accepted July 11, 2015; Epub July 15, 2015; Published July 30, 2015

Abstract: The DNA repair system plays a pivotal role in maintaining genomic integrity and protection against mutations that could lead to cancer development. The aim of this study was to explore the association between common polymorphisms of DNA repair genes, *APE1* (rs1760944 and rs1130409) and *XRCC1* (rs1799782, rs25487, and rs25489), and gastric cancer (GC) risk in the Korean population. We conducted a case-control study of 368 GC patients and 398 controls by using TaqMan genotyping assay. None of the polymorphisms was associated with the risk of GC. Further analysis showed a lack of association between *APE1* and *XRCC1* polymorphisms or haplotypes and the risk of GC and GC subgroups. The heterozygous CT genotype of *XRCC1* rs25487 was related to 1.94 times increased risk of lymph node metastasis (LNM) in diffuse type GC compared to the *XRCC1* rs25487 CC genotype (adjusted OR = 1.94, 95% CI = 1.06-3.53, *P* = 0.031) after adjusting for gender and age, whereas the remaining polymorphisms showed no association with GC or GC subgroups. This result suggests that genetic variation of *XRCC1* rs25487 could be a risk factor for LNM in diffuse type of GC in the Korean population.

Keywords: Gastric cancer, diffuse type, DNA repair, *APE1*, *XRCC1*, lymph node metastasis

Introduction

Gastric cancer (GC) is one of the most common cancers affecting people worldwide. In the past few decades, the incidence and mortality rate of GC have been gradually decreasing, but they continue to be high in Asian countries. Particularly, in Korea, GC is the third-most common cancer, with 34,478 new cases and 7,876 deaths being recorded in 2014, as per the report of the Korea National Cancer Center [1-3].

DNA repair pathways are essential for maintaining genomic integrity and for protecting against mutations that lead to unregulated cell growth, disease, and cancer [4]. There are four major DNA repair pathways, including nucleotide excision repair (NER), base excision repair (BER), double-strand break repair (DSBR), and mismatch repair (MMR). Among DNA repair pathways, the BER pathway is one of the most active DNA repair processes, and is responsible for removing damaged small base lesions [5, 6]. Impaired DNA repair capacity owing to genetic variation in the DNA repair genes is associated with the cancer risk [7-9].

The DNA repair enzymes apurinic/apyrimidinic endonuclease (APE1) and X-ray repair cross-complementing group 1 (XRCC1) play a pivotal role in the BER pathway [10]. *APE1* and *XRCC1* genes are located on chromosomes 19q13.2-13.3 and 14q11.2-q12, respectively. Two common SNPs within *APE1* are rs1760944 (promoter region, base G to T) and rs1130409 (exon5, base T to G, codon 148 Asp/Glu). Three non-synonymous common SNPs in *XRCC1* lead to the amino acid substitutions: rs1799782 (exon6, base G to A, codon 194 Arg/Trp), rs25489 (exon9, base C to T, codon 280 Arg/His), and rs25487 (exon10, base C to T, codon 399 Arg/Gln).

In the past decade, three common single nucleotide polymorphisms (SNPs) of *XRCC1* and two

Table 1. Characteristics of gastric cancer patients and controls enrolled in the study

Variable	Case	Control	*P*
	N (%)	N (%)	
All subjects	368 (100)	398 (100)	
Age (years) (mean ± SD)	60.1 ± 11.9	58.7 ± 9.0	0.069[a]
Gender			
Male	260 (70.7)	132 (33.2)	<0.001[b]
Female	108 (29.3)	266 (66.8)	
Histological type			
Intestinal	192 (52.2)		
Diffuse	138 (37.5)		
Mixed	38 (10.3)		
Lymph node metastasis			
Negative	257 (69.8)		
Positive	111 (30.2)		

[a]Two-sided *t*-test. [b]Two-sided χ^2 test.

common SNPs of *APE1* have been extensively studied for their association with the risk for several types of cancer in diverse populations [11, 12]. Several studies, including meta-analysis, have reported an association between SNPs in *APE1* and *XRCC1* and GC risk, with conflicting results in different populations [13-29]. The only study of a Korean population showed the lack of association between *XRCC1* polymorphisms and GC [19]. Despite reports on the association between two common SNPs of *APE1* and GC risk in different ethnic groups, no studies have evaluated their association with GC risk in a Korean population.

Therefore, we performed an association study to assess whether genetic variations in *APE1* and *XRCC1* affect GC susceptibility in the Korean population.

Materials and methods

Subjects

In total, 368 GC patients and 398 healthy controls were enrolled in this study. The blood samples used in this study were provided by the Chungnam National Hospital Biobank, a member of the National Biobank of Korea, which is supported and audited by the Ministry of Health and Welfare of Korea. All individuals enrolled in this study provided their written informed consent for blood collection and use. The study protocol was approved by the Institutional Review Board of the Chungnam National University Hospital (IRB No. 2013-08-008). GC patients were recruited from the outpatient clinic at the Chungnam National University Hospital, and classified according to the Lauren's classification [30]. The controls were randomly selected among healthy volunteers visiting the Chungnam National University Hospital medical center for their annual physical examinations, and included only those individuals who had no history of cancer.

Genotyping

Genomic DNA was extracted from the peripheral blood by using the QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany), according to the manufacturer's instructions. Genotyping was performed using the Applied Biosystems TaqMan SNP Genotyping Assay and the StepOnePlus Real-time PCR System (Applied Biosystems, Foster City, USA).

Statistical analysis

χ^2 tests were used to estimate the Hardy-Weinberg equilibrium (HWE) of each SNP and to detect age and gender in the GC and control groups. The association between the GC and control groups was analyzed by χ^2 test. We used binary logistic regression to estimate the GC risk using odds ratios (OR) and 95% confidence intervals (CI). ORs were adjusted according to gender and age. All statistical analyses were performed using the SPSS (SPSS Inc., Chicago, IL, USA), version 20.0 for windows. $P < 0.05$ was considered statistically significant.

Results

Characteristics of studies

The characteristics of 368 GC patients (260 male, 108 female) with a mean age of 60.1 ± 11.9 years and 398 healthy controls (132 male, 266 female) with a mean age of 58.7 ± 9.0 years are shown in **Table 1**. No significant difference was found between GC patients and controls with respect to the distribution of age ($P = 0.069$), whereas the distribution of gender among GC patients differed from that of the controls ($P < 0.001$). Out of the 368 GC cases, 192 (52.2%) were classified as an intestinal

Table 2. Genotype and allele frequencies of *APE1* and *XRCC1* polymorphisms among GC patients and controls and their association with GC risk

SNP	Genotype	Controls	GC vs. CON		
		N (%)	N (%)	OR (95% CI)[a]	*P*
APE1					
rs1760944	GG	115 (28.9)	100 (27.2)	1.00 (ref.)	
	GT	196 (49.2)	184 (50.0)	1.12 (0.78-1.60)	0.548
	TT	87 (21.9)	84 (22.8)	1.15 (0.75-1.78)	0.525
Allele	G	426 (53.5)	384 (52.2)	1.00 (ref.)	
	T	370 (46.5)	352 (47.8)	1.08 (0.87-1.34)	0.509
APE1					
rs1130409	TT	132 (33.2)	115 (31.3)	1.00 (ref.)	
	TG	201 (50.5)	177 (48.1)	1.00 (0.71-1.41)	0.986
	GG	65 (16.3)	76 (20.6)	1.45 (0.92-2.27)	0.107
Allele	T	465 (58.4)	407 (55.3)	1.00 (ref.)	
	G	331 (41.6)	329 (44.7)	1.17 (0.94-1.46)	0.160
XRCC1					
rs1799782	GG	170 (42.7)	170 (46.2)	1.00 (ref.)	
	GA	184 (46.2)	154 (41.8)	0.79 (0.57-1.09)	0.153
	AA	44 (11.1)	44 (12.0)	1.08 (0.65-1.79)	0.772
Allele	G	524 (65.8)	494 (67.1)	1.00 (ref.)	
	A	272 (34.2)	242 (32.9)	0.95 (0.76-1.19)	0.657
XRCC1					
rs25489	CC	314 (78.9)	278 (75.5)	1.00 (ref.)	
	CT	77 (19.3)	84 (22.8)	1.20 (0.83-1.75)	0.338
	TT	7 (1.8)	6 (1.7)	1.19 (0.36-3.91)	0.774
Allele	C	705 (88.6)	640 (87.0)	1.00 (ref.)	
	T	91 (11.4)	96 (13.0)	1.17 (0.84-1.63)	0.341
XRCC1					
rs25487	CC	243 (61.1)	222 (60.3)	1.00 (ref.)	
	CT	128 (32.2)	127 (34.5)	1.09 (0.79-1.52)	0.599
	TT	27 (6.7)	19 (5.2)	0.79 (0.41-1.52)	0.475
Allele	C	614 (77.1)	571 (77.6)	1.00 (ref.)	
	T	182 (22.9)	165 (22.4)	0.98 (0.76-1.27)	0.896

SNP, single nucleotide polymorphism; GC, gastric cancer; CON, controls; OR, odds ratio; CI, confidence interval. [a]Adjusted for gender and age.

type, 138 (37.5%) as a diffuse type, and 38 (10.3%) as a mixed type. GC cases comprised of 257 (69.8%) negative cases and 111 (30.2%) positive cases for lymph node metastasis (LNM).

Association between the genotypes and allele frequencies of the SNPs and GC risk

Genotype distributions of two SNPs in *APE1* (rs1130409 and rs1760944) and three SNPs in *XRCC1* (rs1799782, rs25487, and rs25489) in patients and controls are summarized in **Table 2**. The genotype frequencies of five SNPs were found to be in HWE in both GC patients and controls ($P > 0.05$; data not shown). To determine whether *APE1* and *XRCC1* variations were associated with the risk of GC and GC subtypes, we analyzed the genotypes and allele frequencies. We found no association between *APE1* and *XRCC1* genetic polymorphisms and the risk of GC and GC subtypes (**Table 2**, Supplementary Table 1).

Furthermore, we conducted the logistic regression analysis to evaluate the association between *APE1* and *XRCC1* genetic variations and LNM in GC and GC subtypes. The *XRCC1* rs25487 CT genotype was associated with an increased risk of LNM in diffuse type GC (adjusted OR = 1.94, 95% CI = 1.06-3.53, $P = 0.031$) after adjusting for gender and age, whereas the remaining SNPs showed no association (**Table 3**).

In addition, we conducted haplotype analysis to estimate the association of haplotypes of *APE1* (rs1130409 and rs1760944) and *XRCC1* (rs1799782, rs25487, and rs25489) SNPs and GC risk. No statistical association between haplotypes and the risk of GC was observed ($P > 0.05$) (data not shown).

Discussion

In the present study, we investigated the association between two *APE1* SNPs and three *XRCC1* SNPs and GC risk in the Korean population. We found that the *XRCC1* rs25487 heterozygous CT polymorphism was associated with an increased risk of LNM in diffuse type GC.

Thus far, several studies, including meta-analyses, have reported the case-control data evalu-

Table 3. Association of genetic polymorphisms in *APE1* and *XRCC1* with LNM in diffuse type GC

SNP	Genotype	Controls	Diffuse type GC (negative) vs. CON			Diffuse type GC (positive) vs. CON		
		N (%)	N (%)	OR (95% CI)[a]	*P*	N (%)	OR (95% CI)[a]	*P*
APE1								
rs1760944	GG	115 (28.9)	24 (28.2)	1.00 (ref.)		16 (30.2)	1.00 (ref.)	
	GT	196 (49.2)	42 (49.4)	1.16 (0.65-2.07)	0.625	22 (41.5)	0.84 (0.42-1.68)	0.620
	TT	87 (21.9)	19 (22.4)	1.18 (0.59-2.36)	0.643	15 (28.3)	1.28 (0.59-2.76)	0.536
Allele	G	426 (53.5)	90 (52.9)	1.00 (ref.)		54 (50.9)	1.00 (ref.)	
	T	370 (46.5)	80 (47.1)	1.09 (0.77-1.55)	0.621	52 (49.1)	1.13 (0.75-1.70)	0.567
APE1								
rs1130409	TT	132 (33.2)	26 (30.6)	1.00 (ref.)		14 (26.4)	1.00 (ref.)	
	TG	201 (50.5)	43 (50.6)	0.93 (0.53-1.63)	0.789	28 (52.8)	1.21 (0.61-2.40)	0.595
	GG	65 (16.3)	16 (18.8)	1.23 (0.59-2.54)	0.582	11 (20.8)	1.59 (0.68-3.76)	0.287
Allele	T	465 (58.4)	95 (55.9)	1.00 (ref.)		56 (52.8)	1.00 (ref.)	
	G	331 (41.6)	75 (44.1)	1.07 (0.76-1.52)	0.693	50 (47.2)	1.24 (0.82-1.87)	0.315
XRCC1								
rs1799782	GG	170 (42.7)	36 (42.4)	1.00 (ref.)		27 (50.9)	1.00 (ref.)	
	GA	184 (46.2)	40 (47.0)	1.04 (0.62-1.75)	0.887	22 (41.6)	0.77 (0.42-1.42)	0.398
	AA	44 (11.1)	9 (10.6)	1.26 (0.55-2.92)	0.583	4 (7.5)	0.62 (0.20-1.90)	0.405
Allele	G	524 (65.8)	112 (65.9)	1.00 (ref.)		76 (71.7)	1.00 (ref.)	
	A	272 (34.2)	58 (34.1)	1.09 (0.75-1.57)	0.652	30 (28.3)	0.79 (0.50-1.24)	0.299
XRCC1								
rs25489	CC	314 (78.9)	65 (76.5)	1.00 (ref.)		44 (83.0)	1.00 (ref.)	
	CT	77 (19.3)	18 (21.1)	1.07 (0.58-1.98)	0.831	7 (13.2)	0.61 (0.26-1.43)	0.253
	TT	7 (1.8)	2 (2.4)	1.84 (0.36-9.41)	0.467	2 (3.8)	2.36 (0.45-12.51)	0.312
Allele	C	705 (88.6)	148 (87.1)	1.00 (ref.)		95 (89.6)	1.00 (ref.)	
	T	91 (11.4)	22 (12.9)	1.16 (0.69-1.97)	0.580	11 (10.4)	0.88 (0.45-1.72)	0.704
XRCC1								
rs25487	CC	243 (61.1)	59 (69.4)	1.00 (ref.)		25 (47.2)	1.00 (ref.)	
	CT	128 (32.2)	24 (28.2)	0.69 (0.40-1.20)	0.186	26 (49.0)	1.94 (1.06-3.53)	0.031
	TT	27 (6.7)	2 (2.4)	0.30 (0.07-1.34)	0.114	2 (3.8)	0.76 (0.17-3.41)	0.715
Allele	C	614 (77.1)	142 (83.5)	1.00 (ref.)		76 (71.7)	1.00 (ref.)	
	T	182 (22.9)	28 (16.5)	0.62 (0.39-1.02)	0.056	30 (28.3)	1.33 (0.84-2.12)	0.222

SNP, single nucleotide polymorphism; GC, gastric cancer; CON, controls; OR, odds ratio; CI, confidence interval. [a]Adjusted for gender and age.

ating association between genetic variations of *APE1* or *XRCC1* and GC risk in different ethnic groups; however, the results are controversial [13-29]. In case of *APE1* gene, a few investigations have assessed the association between its polymorphisms and GC susceptibility. We observed no association between two of the *APE1* SNPs and GC risk in the Korean population. However, contradictory to our data, Canbay et al. and Gu et al. reported that *APE1* rs1130409 SNP was associated with the GC risk in the Turkish and Chinese populations, respectively [13, 17]. No association in the Italian population was consistent with our findings [14]. Zhao et al. showed that the *APE1* promoter polymorphism rs1760944 was associated with GC survival [15]. In a recent meta-analysis, Dai et al. revealed that *APE1* rs1760944 promoter polymorphism was associated with the protective cancer risk in the Asian population [16]. Reports by both Ratnasinghe et al. and Yan et al. on the negative association between *XRCC1* rs1799782 and GC risk were in agreement with our results [20, 23], whereas Shen et al., Yuan et al., Pan et al., and Wen et al. showed positive associations in the Chinese population [18, 24, 28, 29]. The negative association reported between *XRCC1* rs1799782

and GC risk by Yan et al. and Xue et al. were consistent with our results. In agreement with our present results, case-control studies by Yan et al. and Liu et al. and the meta-analysis by Xue et al. indicated that *XRCC1* rs25487 SNP was not associated with GC risk in the Chinese population [23, 25, 27]. However, Shen et al., Ratnasinghe et al., and Miao et al. revealed positive associations between *XRCC1* rs25487 SNP and GC risk in the Chinese population [18, 20, 22]. In the Brazilian population, Durate et al. reported that rs1799782 and rs25487 SNPs in *XRCC1* were associated with the environmental factor of GC [21]. In the Korean population, Lee et al. observed no association between three non-synonymous SNPs (rs1799782, rs25489, and rs25487) in *XRCC1* and GC risk, similar to our results [19]. Interestingly, we observed an association between *XRCC1* rs25487 SNP and an increased LNM risk in diffuse type GC. Furthermore, Lee at al. showed that the haplotype of these SNPs was associated with the risk of GC and diffused type GC. In contrast, we found no such evidence in the haplotype analysis (data not shown).

There are some limitations to our study. First, the sample size was too small to have a statistical power in the subgroup analysis. Second, although *Helicobacter pylori* is an independent risk factor of GC [31, 32], we did not investigate the association between SNPs in *APE1 and XRCC1* genes and the infection of *Helicobacter pylori* in GC because of an ethical consideration. Third, we did not explore whether there were associations between smoking, drinking, and diet relating GC risks and polymorphisms due to the unavailability of such data for GC and control groups. In our future studies, the effect of these factors on GC risk will be assessed.

In conclusion, our study demonstrated that *XRCC1* rs25487 polymorphism could be an important factor contributing to the increased risk of LNM in diffuse type of GC in the Korean population. Despite the small sample size in subgroup analyses, this finding provides a better understanding of GC development.

Acknowledgements

This research was supported by a grant of the Korea Health Technology R&D Project Ministry of Health & Welfare, Republic of Korea (grant number: HI14C1731), a research fund of Chungnam National University, and Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (grant numbe: NRF- 2014R1A6A1029617).

Disclosure of conflict of interest

None.

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Supplementary Table 1. Genotype and allele frequencies of *APE1* and *XRCC1* polymorphisms among GC patients and controls and their association with the risk of intestinal and diffuse type GC

SNP	Geno-type	Controls	Intestinal type GC vs. CON			Diffuse type GC vs. CON		
		N (%)	N (%)	OR (95% CI)[a]	*P*	N (%)	OR (95% CI)[a]	*P*
APE1								
rs1760944	GG	115 (28.9)	47 (24.5)	1.00 (ref.)		40 (29.0)	1.00 (ref.)	
	GT	196 (49.2)	103 (53.6)	1.36 (0.86-2.15)	0.191	64 (46.4)	1.02 (0.63-1.63)	0.952
	TT	87 (21.9)	42 (21.9)	1.31 (0.75-2.29)	0.341	34 (24.6)	1.18 (0.68-2.06)	0.555
Allele	G	426 (53.5)	197 (51.3)	1.00 (ref.)		144 (52.2)	1.00 (ref.)	
	T	370 (46.5)	187 (48.7)	1.15 (0.88-1.51)	0.311	132 (47.8)	1.09 (0.82-1.44)	0.564
APE1								
rs1130409	TT	132 (33.2)	62 (32.3)	1.00 (ref.)		40 (29.0)	1.00 (ref.)	
	TG	201 (50.5)	92 (47.9)	0.90 (0.59-1.39)	0.639	71 (51.4)	1.08 (0.68-1.71)	0.744
	GG	65 (16.3)	38 (19.8)	1.47 (0.84-2.60)	0.182	27 (19.6)	1.36 (0.76-2.46)	0.304
Allele	T	465 (58.4)	216 (56.3)	1.00 (ref.)		151 (54.7)	1.00 (ref.)	
	G	331 (41.6)	168 (43.7)	1.15 (0.88-1.51)	0.316	125 (45.3)	1.15 (0.86-1.53)	0.345
XRCC1								
rs1799782	GG	170 (42.7)	90 (46.9)	1.00 (ref.)		63 (45.7)	1.00 (ref.)	
	GA	184 (46.2)	76 (39.6)	0.75 (0.50-1.13)	0.163	62 (44.9)	0.89 (0.58-1.36)	0.585
	AA	44 (11.1)	26 (13.5)	1.29 (0.69-2.40)	0.421	13 (9.4)	0.95 (0.47-1.92)	0.887
Allele	G	524 (65.8)	256 (66.7)	1.00 (ref.)		188 (68.1)	1.00 (ref.)	
	A	272 (34.2)	128 (33.3)	1.00 (0.75-1.33)	0.979	88 (31.9)	0.94 (0.70-1.28)	0.709
XRCC1								
rs25489	CC	314 (78.9)	147 (76.6)	1.00 (ref.)		109 (79.0)	1.00 (ref.)	
	CT	77 (19.3)	44 (22.9)	1.12 (0.71-1.79)	0.625	25 (18.1)	0.93 (0.55-1.56)	0.772
	TT	7 (1.8)	1 (0.5)	0.41 (0.04-3.92)	0.436	4 (2.9)	2.07 (0.58-7.39)	0.262
Allele	C	705 (88.6)	338 (88.0)	1.00 (ref.)		243 (88.0)	1.00 (ref.)	
	T	91 (11.4)	46 (12.0)	1.02 (0.67-1.56)	0.917	33 (12.0)	1.09 (0.70-1.69)	0.694
XRCC1								
rs25487	CC	243 (61.1)	111 (57.8)	1.00 (ref.)		84 (60.9)	1.00 (ref.)	
	CT	128 (32.2)	67 (34.9)	1.14 (0.75-1.72)	0.534	50 (36.2)	1.07 (0.70-1.63)	0.767
	TT	27 (6.7)	14 (7.3)	1.39 (0.65-3.00)	0.398	4 (2.9)	0.42 (0.14-1.27)	0.124
Allele	C	614 (77.1)	289 (75.3)	1.00 (ref.)		218 (79.0)	1.00 (ref.)	
	T	182 (22.9)	95 (24.7)	1.17 (0.85-1.61)	0.326	58 (21.0)	0.87 (0.61-1.22)	0.414

SNP, single nucleotide polymorphism; GC, gastric cancer; CON, controls; OR, odds ratio; CI, confidence interval. [a]Adjusted for gender and age.