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Cancer Letters 187 (2002) 53–60

CANCER Letters

www.elsevier.com/locate/canlet

Genetic polymorphisms of *XRCC1* and risk of gastric cancer

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Received 8 March 2002; received in revised form 19 June 2002; accepted 20 June 2002

Abstract

Coding polymorphisms of the DNA repair gene *XRCC1* have been shown to affect the DNA repair capacity and to be associated with genetic susceptibility to carcinogenesis. In our association study between three amino acid substitution polymorphisms of *XRCC1* (Arg194Trp, Arg280His, and Arg399Gln) and the risk of gastric cancer in the Korean population, none of the polymorphisms were associated with increased risk of gastric cancer. We then extended our study by building haplotypes of the entire *XRCC1* gene with six single neuclotide polymorphisms (SNPs), including two novel polymorphisms at the 5′-flanking sequence. When haplotype frequencies in cases and controls and haplotype-specific odds ratios (ORs) were estimated, haplotype A (194Trp, 280Arg, and 399Arg) was associated with significant reduction in gastric cancer risk (adjusted OR = 0.65, 95% CI = 0.43–0.99) whereas haplotype D (194Arg, 280Arg, and 399Arg alleles) was a risk type for gastric cancer (adjusted OR = 1.57, 95% CI = 0.93–2.65). The association with the haplotype D was more pronounced in the cancers of antrum (adjusted OR = 2.06, 95% CI = 1.03–2.00). Our results suggest that the haplotype estimation is advantageous for association studies of such a complex disease as gastric cancer.

Keywords: Association study; Gastric cancer; *XRCC1*; Polymorphism; Haplotype

1. Introduction

Gastric cancer is one of the most commonly diagnosed malignancies of the worldwide population and the first cause of cancer deaths in the Korean population. The risk of gastric cancer has been associated with various exogenous chemicals, dietary habits [1], *Helicobactor pylori* infection [2], and genetic factors [3]. The pathological changes due to host inflammatory responses against infectious agents are also risk factors for gastric carcinogenesis [4]. Many kinds of genetic alterations including mutation, over-expression, and instability are responsible for the development and progression of gastric cancer [3]. Recently, three coding polymorphisms of DNA repair gene *XRCC1* have been identified in healthy individuals [5]. They include non-conservative amino acid substitutions of arginine for tryptophan at codon 194 (Arg194Trp), arginine for histidine at codon 280 (Arg280His), and arginine for glutamine at codon 399 (Arg399Gln). These amino acid substitutions occur in evolutionarily conserved regions, suggesting

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0304-3835/02/$ - see front matter
PII: S0304-3835(02)00381-6

potential functional significance. Subsequent studies have shown that the 399Gln allele is associated with higher levels of aflatoxin DNA adducts and glycophorin NN mutations in placental DNA [6] and higher level of sister chromatid exchanges (SCEs) in human lymphocytes [7,8].

A number of population-based case–control studies have examined the association between *XRCC1* polymorphisms and cancer susceptibility. Depending on ethnic groups and cancer types, the risk genotype of *XRCC1* has been rather controversial. In the previous lung cancer studies, positive associations were reported with the *XRCC1* 399Gln allele in non-Hispanic Caucasians [9] and with 280His allele in Chinese miners [10]. However, in an African–American population, the 399Gln and 194Trp alleles were associated with the decreased risk of lung cancer [11]. In an association study between *XRCC1* polymorphisms and gastric cancer risk in a Chinese population, 194Arg homozygote and 399Arg/Gln and/or Gln homozygote were the risk genotypes of gastric carcinogenesis [12].

In this study, we have conducted an association study of the reported *XRCC1* polymorphisms with the gastric cancer in the Korean population. We then have extended our study by building haplotypes of the entire *XRCC1* gene covering 25.5 kb. It was shown that certain haplotypes were associated with gastric cancer either positively or negatively, whereas no association was found with individual polymorphism.

2. Materials and methods

2.1. Study subjects

Subjects were diagnosed as having gastric adenocarcinomas by gastroscopic biopsies between November 30, 1999 and November 29, 2001 at Asan Medical Center, Seoul, South Korea. Of the 1200 cases referred for surgery during this period, 368 subjects were enrolled in the study voluntarily; the participation rate was 30.7%. From the enrolled pool, a total of 190 gastric cancer cases and 172 age and sex frequency matched controls were included in this hospital-based case–control study. The rest of the 178 subjects with gastric carcinoma were not included in this study, because no age/sex-matched controls were available. The controls were cancer-free individuals stratified and frequency matched with age and sex from the Health Promotion Center of the hospital where routine physical check-ups were done. This study was approved by the Ethical Committee of Asan Medical Center.

Gastric cancers were classified as diffuse and intestinal types according to the Laurén's classification [13]. In diffuse types, cancer cells did not tend to form glands or tight clusters as was seen in intestinal type carcinomas frequently. The diffuse type cells often contained mucin in the cytoplasm. Gastric cancers subjects were also categorized according to the location of cancer, i.e. antrum, fundus, and cardia. In the Korean population, gastric cancers develop more frequently in the antrum than in the body, and cardia cancers are comparatively infrequent [14]. It has been suggested that the various topographical predilection of gastric cancer among the populations may reflect different biological backgrounds including genetic differences of the populations [15].

2.2. Single neuclotide polymorphism (SNP) genotyping

DNA was isolated from blood samples using standard procedures. The polymorphisms were analyzed by polymerase chain reaction (PCR) combined with restriction fragment length polymorphism (RFLP) assays or DNA sequencing. PCR and DNA sequencing methods were described elsewhere [16]. The Arg194Trp and Arg399Gln alleles were analyzed by RFLP, whereas the Arg280His allele was analyzed by DNA sequencing. Primer sequences for these variants are available upon request. The restriction enzyme *Pvu*II (MBI Frementas, Hanover, MD) distinguished 194Trp allele as 216 and 123 bp digestion products, and *Msp*I (MBI Frementas, MD) distinguished 399Arg allele as 161 and 146 bp digestion products.

To identify additional SNPs in the 5′-flanking region, 2149 bp ($-1968 \sim 181$) region was amplified with three primer sets and sequenced in 48 healthy individuals. The ATG translation start site was designated as $+1$ (GenBank accession no. L34079). The sequencing traces were analyzed and two novel polymorphisms were identified: -1678 (C → T) and -1449 (ins → del). The allele frequencies of both -1678T and -1449del in 48 individuals were 0.06.

These novel polymorphisms were PCR amplified in a 737 bp fragment: forward primer 5′-CCTTTACCCT-TGGCCTCTTC-3′ and reverse primer 5′-GCACAT-GAAGAGAGGGGAAG-3′ and genotyped by DNA sequencing.

2.3. Statistical analysis

The genotype frequencies were checked for consistency among controls with those expected from Hardy–Weinberg equilibrium. The association between cases and controls were examined by chi-square test for sex and age. The logistic regression analysis was used to adjust for age and sex to calculate ORs and 95% confidence intervals (CIs). For the analysis of association between haplotypes and the gastric cancer risk, binary logistic regression analysis was used.

Polytomous logistic regression for generalized logit model was used to examine association of *XRCC1* polymorphisms with histological type and topographical location. Chromosome numbers for each haplotype were counted manually according to the predicted haplotypes from EMPLUS program [17]. The data were analyzed using the SAS Version 6.12 (SAS institute, Cary, NC).

3. Results and discussion

3.1. XRCC1 coding polymorphisms and gastric cancer risk

As shown in Table 1, all tested cases and controls were well matched for sex and age ($P = 0.82$). The mean age of gastric cancer patients was 51.3 years (range 27–74 years), and the mean age of control group was 50.3 years (range 28–74 years). The allele frequencies of three polymorphisms, Arg194Trp, Arg280His, and Arg399Gln, were not statistically different between the cases and controls (Table 2). The frequencies of 194Trp or 399Gln homozygotes were similar in the cases and controls (8.4 and 8.1%, 4.7 and 5.2%, respectively) and were not associated with a risk of gastric cancer with adjustment for age and sex (adjusted OR = 0.82, 95% CI = 0.37–1.79; adjusted OR = 0.88, 95% CI = 0.33–2.31,

Table 1
Clinicopathologic characteristics

	Patients ($n = 190$)		Controls ($n = 172$)		P[a]
	N	%	*N*	%	
Sex					0.82
Male	116	61.1	103	59.9	
Female	74	38.9	69	40.1	
Age (years)					
≤ 45	61	32.1	58	33.7	
46–55	62	32.6	54	31.4	
56–65	50	26.3	45	26.2	
> 65	17	8.9	15	8.7	
Mean ± SD	51.3 ± 10.5		50.3 ± 11.5		
Stratification of patients by histological type and topographical location					
Histological type					
Diffuse type	153	80.5			
Intestinal type	28	14.7			
Unclassified type	9	4.7			
Topographical location					
Body	89	46.8			
Antrum	66	34.7			
Body and antrum	7	3.7			
Others	28	14.7			

[a] Chi-square test for sex.

Table 2
Gastric cancer risk for *XRCC1* genotypes

Locus	Cases ($n = 190$)		Controls ($n = 172$)		Adjusted OR (95% CI)[b]
	N	%	*N*	%	
Exon 6, codon 194					
Arg/Arg	99	52.1	72	41.9	1.00 [c]
Arg/Trp	75	39.5	86	50.0	0.64 (0.41–0.98) [c]
Trp/Trp	16	8.4	14	8.1	0.82 (0.37–1.79) [c]
Arg/Arg	99	52.1	72	41.9	1.00
Arg/Trp & Trp/Trp	91	47.9	100	58.1	0.66 (0.44–1.00)
Exon 9, codon 280					
Arg/Arg	139	73.2	137	79.7	1.00
Arg/His	48	25.3	35	20.3	1.36 (0.83–2.24)
His/His	3	1.6	0		NC[a]
Arg/Arg	139	73.2	137	79.7	1.00
Arg/His & His/His	51	26.8	35	20.3	1.45 (0.89–2.37)
Exon 10, codon 399					
Arg/Arg	110	57.9	94	54.7	1.00 [d]
Arg/Gln	71	37.4	69	40.1	0.89 (0.58–1.37) [d]
Gln/Gln	9	4.7	9	5.2	0.88 (0.33–2.31) [d]
Arg/Arg	110	57.9	94	54.7	1.00
Arg/Gln & Gln/Gln	80	42.1	78	45.3	0.89 (0.58–1.34)

[a] NC, not calculated.
[b] Adjusted for age and sex.
[c] There was no difference in the Arg194Trp distributions between cases and controls ($P = 0.123$).
[d] There was no difference in the Arg399Gln distributions between cases and controls ($P = 0.849$).

respectively). However, with the Arg194Arg genotype as the reference group, the combined genotype (Arg194Trp and Trp194 Trp) – specific odds ratio was 0.66 (95% CI = 0.44–1.00, $P = 0.052$), suggesting that 194Trp allele might be a protective allele for gastric cancer. The Arg280His polymorphism was not associated with gastric cancer risk (adjusted OR = 1.36, 95% CI = 0.83–2.24). The combined genotype (Arg280His and His280His) – specific OR 1.45 (95% CI = 0.89–2.37, $P = 0.140$), which was slightly elevated but not statistically significant.

3.2. Identification of additional SNPs for building XRCC1 haplotypes

The human *XRCC1* gene consists of 17 exons and spans over 33 kb in the chromosome 19q13.2 region [18]. The tested polymorphisms of *XRCC1* were located in exons 6, 9, and 10 and covered approximately 1.9 kb. To build haplotypes of the entire *XRCC1* gene, we searched for the additional candidate SNPs from dbSNP (www.ncbi.nlm.nih.gov/SNP). Of 21 SNPs retrieved, only one was located in exon 16 (Asn576Tyr). When the Asn576Tyr allele was genotyped in 96 individuals, all of them had 576Tyr. The other candidate SNPs were screened and their allele frequencies were determined in 24 individuals by using a pooled DNA sequencing method [16]. Of those screened, only one, 14223 (G → A) polymorphism in intron 2, showed minor allele frequency greater than 0.2, and, thus was included in further genotyping with study subjects. Its minor allele frequency in the 172 individuals was 0.39.

There was no polymorphism reported from the 5′-flanking region of *XRCC1* in the public database. We identified two novel polymorphisms at nt −1678 (C → T) and nt −1449 (ins → del). The newly identified two polymorphisms in the 5′-flanking region were in the putative transcription factor binding sites; the −1678C allele in the SP1 binding site and the

−1449ins allele in the GCF binding site, respectively. These polymorphisms were completely linked and allele frequencies of both −1678C and −1449ins were 0.91. The 5′-flanking region of the baboon *XRCC1*, which showed 93% identity with those of human *XRCC1*, has shown promoter activity in transient transfection assays [19]. Further study is needed to characterize functional significance of the 5′-flanking polymorphisms on transcriptional activity of the human *XRCC1* gene.

3.3. Association analysis between XRCC1 haplotype and gastric cancer risk

EMPLUS program was used to infer haplotypes and haplotype frequencies in controls and cases. Without examining family samples for inheritance patterns, the precise accuracy of this inference method is not known. The EM algorithm predicted nine different haplotypes in 344 chromosomes. Of the nine, six haplotypes (A–F) accounted for 99% of all those seen. The rest with frequencies smaller than 1% were excluded because of possible genotyping errors. The accuracy of this inference method is not known. The SNP composition of individual haplotype is shown in Table 3. The most common haplotype A carried 194Trp, 280Arg, and 399Arg alleles, the second most common haplotype B carried 194Arg, 280Arg, and 399Gln alleles, and haplotype E carried 194Arg, 280His, and 399Arg alleles. The haplotypes, C, D, and F carried Arg alleles at all three codons, but different alleles at the rest of SNP sites. The haplotypes A, D, and E all carried −1678C, −1449ins, and 14233G, but different amino acids at three codons.

The haplotype distribution in the controls and cases is shown in Table 3. Combined frequency of the three dominant haplotypes (A, B, and C) was over 70%. The haplotypes showing significant differences in the estimated haplotype frequencies between the cases and controls were chosen for further risk assessment in logistic regression analysis (haplotypes A, D, and E). Statistically significant results were found only in two haplotypes, A and D.

The haplotype A was the most frequent one in the cases as well as controls and had functional variant at codon 194. Its frequency was increased in the controls (32.8%) compared with the cases (27.6%). When OR was estimated for individuals carrying both and one of the haplotype A versus none of the haplotype A, it appeared to be associated with significant reduction in gastric cancer risk (adjusted OR = 0.65, 95% CI = 0.43–0.99) (Table 4). Statistically significant reduction was observed for diffuse type gastric cancer as well (adjusted OR = 0.62, 95% CI = 0.63–0.98). Similar result was shown in the individual genotype analysis of the 194Trp allele (Table 2), suggesting the biological significance of the particular allele in the carcinogenesis. This result was consistent with

Table 3
Distribution of the estimated haplotype frequencies for *XRCC1* in controls and gastric cancer cases

Haplotype[a]	Loci	Controls	All cases	Diffuse type gastric cancer	Gastric antral cancer
		N (%)	*N* (%)	*N* (%)	*N* (%)
No. of chromosome[b]		344 (100)	380 (100)	306 (100)	132 (100)
Location[c]	(-1678) (-1449) (14223) codon 194 codon 280 codon 399				
A	C–ins–G–Trp–Arg–Arg	113 (32.8)	105 (27.6)	85 (27.8)	32 (24.2)
B	C–ins–A–Arg–Arg–Gln	86 (25.0)	86 (22.6)	68 (22.2)	26 (19.7)
C	C–ins–A–Arg–Arg–Arg	47 (13.7)	50 (13.2)	38 (12.4)	25 (18.9)
D	C–ins–G–Arg–Arg–Arg	29 (8.4)	48 (12.6)	38 (12.4)	21 (15.9)
E	C–ins–G–Arg–His–Arg	33 (9.6)	52 (13.7)	42 (13.7)	19 (14.4)
F	T–del–G–Arg–Arg–Arg	30 (8.7)	31 (8.2)	27 (8.8)	9 (6.8)

[a] Haplotypes were estimated from unphased genotypes by using EMPLUS program [17].
[b] Chromosome numbers for each haplotype were counted manually based on the predicted haplotypes from EMPLUS program.
[c] Nucleotide number is based on the first nucleotide of the ATG start codon being +1 (GenBank accession no. L34079).

Table 4
Logistic regression analysis of *XRCC1* haplotypes and gastric cancer risk

Haplotype	Controls	All cases		Diffuse type gastric cancer		Gastric antral cancer	
	N (%)	*N* (%)	Adjusted OR[a] (95% CI)	*N* (%)	Adjusted OR[a] (95% CI)	*N* (%)	Adjusted OR[a] (95% CI)
All subjects	172 (100)	190 (100)		153 (100)		66 (100)	
Haplotype A							
−/−	73 (42.4)	101 (53.2)	1.00	83 (54.2)	1.00	36 (54.5)	1.00
A/− & A/A	99 (57.6)	89 (46.8)	0.65 (0.43–0.99)**	70 (45.8)	0.62 (0.63–0.98)**	30 (45.5)	0.61 (0.59–1.04)*
Haplotype D							
−/−	143 (83.1)	144 (75.8)	1.00	117 (76.5)	1.00	46 (69.7)	1.00
D/− & D/D	29 (16.9)	46 (24.2)	1.57 (0.93–2.65)*	36 (23.5)	1.51 (0.93–1.62)	20 (30.3)	2.06 (1.03–2.00)**
Haplotype E							
−/−	139 (80.8)	141 (74.2)	1.00	113 (73.9)	1.00	48 (72.7)	1.00
E/− & E/E	33 (19.2)	49 (25.8)	1.48 (0.89–2.44)	40 (26.1)	1.52 (0.95–1.60)	18 (27.3)	1.64 (0.92–1.79)

[a] Adjusted for age and sex. *, $P < 0.1$; **, $P < 0.05$.

the previous study performed in an African–American population showing that the 194Trp allele was associated with the decreased risk of lung cancer [11]. It needs to be confirmed in larger samples whether the 194Trp allele is a protective genotype for gastric cancer indeed.

The haplotypes D and E were more prevalent in the cases (12.6 and 13.7%) than in controls (8.4 and 9.6%). The haplotype D was composed of the most common alleles of all six markers and it differed from haplotype E only at codon 280. Statistically, however, only haplotype D showed significant results whereas haplotype E, which appeared to be a marginal risk haplotype for gastric cancer (adjusted OR = 1.48, 95% CI = 0.89–2.44), was not significantly associated with $P < 0.1$. When an OR was estimated for individuals carrying both and one of the haplotype D versus none of the haplotype D, it appeared to be a putative risk haplotype for gastric cancer (adjusted OR = 1.57, 95% CI = 0.93–2.65). The association of the haplotype D with cancer risk was more prominent in the antral cancer group (adjusted OR = 2.06, 95% CI = 1.03–2.00). In the Korean population, gastric cancer incidence is much higher in the antrum than in the fundus [14]. The antral predilection of gastric cancer correlates with the topographical incidence and intensity of *H. pylori* in the Korean population (Lee et al., submitted for publication). Although the pathobiology of the gastric carcinogenesis remains to be elucidated, the stronger association of the haplotype D with antral cancers in the Korean population supports the biological significance of the association.

In our study, the risk haplotype was haplotype D, having 194Arg and 399Arg alleles. Our results appear to be contradictory to the association study in Chinese population [12]. In the Chinese population, the 194Arg and 399Gln alleles were associated with an increased risk for gastric cancer, particularly for gastric cardia cancer. The discrepancy may have reflected different cancer types in the studies. In the Chinese population, the majority of gastric cancers are cardia cancers, which are infrequent in the Korean population. It has been suggested that cardia cancers may have distinct pathogenesis from antral and body cancers: non-cardia cancers were associated with *H. pylori* infection whereas cardia cancers were not [20]. Ethnic differences may also have contributed to the discrepancy of the two populations.

In this study, we were able to reveal the protective as well as risk haplotypes of *XRCC1* in the Korean gastric cancer subjects in detail. This study is limited by the relatively small number of subjects and needs to be validated by large-scale studies. It needs further investigation to characterize the functional significance of *XRCC1* polymorphisms and susceptibility to carcinogenesis.

Acknowledgements

We thank Drs Jun Ohashi and Boyoul Choi for valuable discussions regarding statistical analysis and an anonymous reviewer for constructive suggestions on the manuscript. This work was supported by the grants to K.S. from the Functional Analysis of Human Genome Project in the 21C Frontier R&D Program of MOST (Ministry of Science and Technology of Korea) and to K.S. and S.L. (#2002-297) from the Asan Institute for Life Sciences, Seoul, South Korea.

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