Possible Associations of *APE1* Polymorphism with Susceptibility and HOGG1 Polymorphism with Prognosis in Gastric Cancer

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Abstract. *Background: Multiple genetic and epigenetic alterations in several genes are implicated in the multistep process of human gastric carcinogenesis. In this study, we examined the polymorphisms of six DNA repair genes: APE1, HOGG1, XRCC1, XRCC3, XPD, and XPG in patients with gastric cancer (GC). Patients and Methods: Forty patients with GC and 247 controls were included in this study. DNA polymorphisms were determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) method. Results: The frequency of the Asp/Glu genotype and Glu allele of APE1 in patients with GC was significantly higher than in the control group (p=0.05). We also observed a higher frequency of the Ser/Ser genotype of HOGG1 in grade III tumors, and in tumors with metastasis to adjacent tissue and solid organs (p<0.05). Conclusion: Our results suggest that (i) APE1 gene polymorphism may be associated with GC risk and (ii) HOGG1 gene polymorphism may be informative in the prognosis of GC.*

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer death worldwide (1). Epidemiological studies have suggested that exogenous factors such as tobacco use, a diet poor in fruits and vegetables or rich in salt, and *Helicobacter pylori* infection increase the risk of GC (2, 3). In addition to above exogenous factors, genetic polymorphisms in the carcinogen detoxification, antioxidant protection, DNA repair and cell proliferation processes are also crucial in the development of GC (4, 5). Genetic polymorphism describes the differences in both the coding and noncoding portions of our DNA and is what makes each of us unique. It can also contribute to our personalized susceptibility to disease. Exhaustive analysis of human single nucleotide polymorphisms (SNPs) has led to the identification of interesting SNP markers for certain disorders such as cancer. There are five major DNA repair pathways: direct repair, base excision repair (BER), nucleotide excision repair (NER), mismatch repair, and double-strand break repair (DSBR), and more than 70 genes in humans are involved in these pathways (6). Enzymes in BER (*e.g.* 8-oxoguanine DNA glycosylase (*HOGG1*), apurinic/apyrimidine endouclease 1 (*APE1*), and X-ray repair cross-complementing group 1 protein (*XRCC1*), remove simple base modifications, such as single-strand breaks, non-bulky adducts, oxidative DNA damage, alkylation adducts and damage induced by ionizing radiation (7, 8). NER enzymes (*e.g. XPD/ERCC2, XPG/ERCC5*) remove more complex, bulky lesions, often caused by environmental agents (*e.g.* polycyclic aromatic hydrocarbons and arylamines) or UV light (9, 10); and have also been associated with the repair of oxidative stress (11, 12). *XRCC3* acts in the homologous recombination repair of DNA double-strand breaks (DDSB), generated by replication errors, endogenous and exogenous agents (13, 14).

There is intensive research focused on the association of DNA repair gene polymorphisms and development of GC. However, the contribution of genetic variations in DNA repair genes to GC risk remains essentially unknown. As a BER gene, *HOGG1* did not show any significant association with GC risk (15). *XRCC1* Arg399Gln variant genotype was found to be associated with reduced risk of cardiac GC in a Chinese population (16), while no association was found in

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other studies (17, 18). It has been found that *XPD* and *XRCC3* variants were not associated with GC risk (19). On the other hand, the frequency and clinical relevance of *XPG* and *APE1* gene polymorphisms in GC has not been determined previously. The aim of this study was to determine the association of polymorphic variants (SNPs) of six DNA repair genes: *APE1* (Asp148Glu), *XRCC1* (Arg399Gln), *XRCC3* (Thr241Met), *XPG* (Lys751Gln), *XPD* (Asp1104His), and *HOGG1* (Ser326Cys) with development, clinical, and histopathological characteristics of GC in a Turkish population.

Patients and Methods

Study group. The patient group consisted of 40 GC patients aged 60.07 (37-81) years who underwent surgical treatment for resectable GC at the Istanbul University Istanbul Medical Faculty, Department of General Surgery, Gastrointestinal Surgery Services. Classification of histological type and tumor stage of the samples were determined according to the International Union Against Cancer (UICC) (20). The control group consisted of age- and sex-matched healthy individuals. The controls were randomly selected from volunteer blood donors. Those with a personal or family history of any cancer and chronic diseases such as cardiovascular or cerebrovascular disease, diabetes mellitus, hypertension, and renal disease were excluded. Controls were also not taking any regular medication. Two hundred and forty-seven healthy controls, with a median age of 52.8 years and an age range of 25-80 years were used as the control group. Informed consent was given by all participants. Questionnaires, medical records, and pathological reports were received to confirm the diagnosis and cancer status. This study protocol was approved by the Local Ethical Committee at Istanbul Medical Faculty, Istanbul University.

DNA isolation and genotyping. Genomic DNA was extracted from whole blood by a simple salting-out procedure (21). The extracted DNA was used for characterization of the following polymorphic DNA repair genes. Polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) was used for genotyping.

Briefly, the polymorphism in *APE1* exon 5 T/G 148 Asp/Glu was determined using the PCR conditions and suitable primers as were described previously (22). The 164-bp PCR product was digested with the *Fsp*BI (MaeI) restriction enzyme at 37˚C for 2 h- and seperated on 3% agarose gel. The restricted products of *APE1* codon 148 Asp/Asp, Asp/Glu, and Glu/Glu genotypes are represented by band sizes of 164, 164/144/20, and 144/20 bp, respectively.

For the *HOGG1* (Ser326Cys) genotyping, PCR condition and primers were used as described previously (23). The 200-bp PCR products were digested with *Fnu*4HI; and seperated on 3% gel; the Cys allele was cut into two 100 bp fragments, while Ser allele was uncut.

The *XRCC1* Arg399Gln polymorphism was determined using PCR condition and primers described by Yeh *et al*. (24). The PCR products (485 bp) were digested overnight with the restriction enzyme *PvuII*. The restricted products of *XRCC1* codon 194 Arg/Arg, Arg/Trp, and Trp/Trp genotypes had band sizes of 485, 485/399/194, and 399/194 bp, respectively.

The *XRCC3* Thr241Met polymorphism, a T→C transition in exon 7 (position 18067), was determined using PCR condition and primers previously described (24). The 456-bp PCR product was digested with Hsp92 (*NIaIII*) restriction enzyme at 37˚C for 6 h; the Met allele was cut into 315-bp and 141-bp fragments, while the Thr allele was uncut.

The *XPD* Lys751Gln polymorphism, a transversion A→C in exon 23 (position 35931), was determined with PCR and primers as described previously (24). The 734-bp PCR product was digested with *PstI*; and the Gln allele was cut into two 646- bp and 88-bp fragments, while the Lys allele was uncut.

The *XPG* (Asp1104His) genotyping was determined with PCR conditions and primers previously established (25). The 271-bp PCR products were digested with *NIaIII*; the C allele was cut into 227-bp and 44-bp fragments, while the G allele was uncut.

Statistical analysis. Statistical analyses were conducted using the SPSS version 13 software package (SPSS Inc., Chicago, IL, USA). Distributions of genotypes and haplotypes were compared by chi-square test. Linkage disequilibrium between *APE1, XRCC1, XRCC3, XPD, XPG,* and *HOGG1* polymorphisms was assessed using D0 and r values obtained through the Haploview program (http://www.broad.mit.edu/mpg/haploview/documentation.php). Data are expressed as the mean±standard deviation (SD). A univariate analysis was performed to compare the distribution of age and gender and the frequencies of alleles and genotypes. A multivariate logistic regression model was performed to investigate possible independent effects of the DNA repair gene genotypes, patient characteristics and clinicopathological parameters after adjustment for age. *P*-value less than 0.05 were considered statistically significant.

Results

Characteristics of patients and primary tumors. Patients and primary tumor characteristics are shown in Table I. The median age was 60.07 (37-81) years. Ten patients (25%) were diagnosed with stage I (n=3) or IIA and IIB (n=7) disease, whereas 30 patients (75%) were diagnosed with stage III (n=14) or IV (n=16) disease. In the pathological assessment of the tumors, the majority (62.5%) of the tumors were poorly (50.5%) or intermediately differentiated (12%) adenocarcinoma with stage III/IV gastric cancer.

Association between the DNA repair genes and patient characteristics. Table II summarizes the distributions of *APE1, XRCC1, XRCC3, XPD, XPG*, and *HOGG1* genotypes and alleles in patients with GC and the controls. The distributions of the genotypes and alleles of the study groups were in Hardy-Weinberg equilibrium. In the present study, the frequencies of the *HOGG1, XRCC1, XRCC3, XPG,* and *XPD* genetic variants were comparable in GC patients and healthy controls in univariate analysis ($p>0.05$, Table II).

We found that the frequencies of Asp/Glu genotype and the Glu allele of *APE1* were significantly higher in GC than in controls (44.4% *vs*. 25.8%, $p<0.05$, odds ratio (OR): 2.3, 95% confidience interval (CI):1-4.9; 63.9% *vs*. 36.1%, $p=0.05$, OR:2.78, 95%CI: 1.3-5.9, respectively, Table II).

Table I. *Characteristics of patients with gastric cancer and controls.*

Parameters	Patients (n=40)		Controls (n=247)	
	N	%	N	%
Age distribution (years)				
≤40	1	2.5	43	17.4
40-60	17	42.5	97	39.3
≥60	22	55	107	43.3
Smoking status				
Yes	25	62.5	91	36.8
No	15	37.5	156	63.2
Alcohol consumption				
Yes	27	67.5	36	14.6
No	13	22.5	211	85.4
T stage				
T1	3	7.5		
T2	8	20		
T3	10	25		
T4	19	47.5		
Lymph node status				
N0	4	10		
N1	8	20		
N2	11	27.5		
N3	17	42.5		
Grade				
Grade I	7	17.5		
Grade II	9	22.5		
Grade III	22	55		
Distant metastasis				
Liver and adjacent tissue	15	37.5		
No	25	62.5		

Table II. *Genotypes and allele frequencies for DNA repair genes in gastric cancer patients and controls.*

Genotype/Alleles	Patients (n=40) %	N	Controls (n=247) %	N	Significance (*p*-value)
APE Asp148Glu					
Asp/Asp	35	14	61.13	151	
Asp/Glu	45	18	25.50	63	
Glu/Glu	20	8	13.36	33	0.007* χ^2; 9.78
Asp	57.5	46	73.88	365	
Glu	42.5	34	26.11	129	0.002 χ^2; 9.09
XRCC1 Arg399Gln					
Arg/Arg	90	36	81.7	202	
Arg/Gln	10	4	17.4	43	
Gln/Gln	0	0	0.8	2	0.41
Arg	95	76	90.4	447	
Gln	5	4	9.5	47	0.18
XRCC3 Thr241Met					
Thr/Thr	40	16	29.9	74	
Thr/Met	47.5	19	59.1	146	
Met/Met	12.5	5	10.9	27	0.36
Thr	63.75	51	59.51	294	
Met	36.25	29	40.48	200	0.47
XPD Lys751Gln					
Lys/Lys	35	14	41.29	102	
Lys/Gln	45	18	46.1	114	
Gln/Gln	20	8	12.5	31	0.41
Lys	57.5	46	64.37	318	
Gln	42.5	34	35.62	176	0.23
XPG Asp1104His					
Asp/Asp	62.5	25	59.9	148	
Asp/His	30	12	33.6	83	
His/His	7.5	3	6.47	16	0.89
Asp	77.5	62	6.72	379	
His	22.5	18	23.27	115	0.87
HOGG1 Ser326Cys					
Ser/Ser	60	24	69.2	171	
Ser/Cys	32.5	13	27.9	69	
Cys/Cys	7.5	3	2.83	7	0.24
Ser	76.25	61	83.19	411	
Cys	23.75	19	16.80	83	0.13

p-Value obtained by Chi-square test, *$p<0.05$.

In the subgroup analysis, the Ser/Ser genotype of *HOGG1* was more frequent in patients with poorly differentiated GC, and in those with metastasis to adjacent tissue or distant tissue than those without (77.3% *vs*. 30.8%; $p<0.05$; OR: 7.65, 95% CI: 1.63-35.79, 84.6% *vs*. 15.4%; $p<0.02$; OR: 6.5, 95% CI: 1.17-35.83, Table III). For tumor site, we found no allelic or genotype differences of any of the genes coding for the selected DNA repair proteins between the tumors located in cardia, corpus and antrum ($p>0.05$, data not shown).

There was no linkage disequilibrium between *APE1, XRCC1, XRCC3, XPD, XPG* and *HOGG1* polymorphisms (D0: 0.014, r^2: 0.005).

Discussion

Genetic variations in DNA repair genes can modulate DNA repair capacity and consequently alter cancer risk. Intensive research has focused on DNA polymorphism and gastric cancer, however, the association of the DNA repair gene polymorphisms with development of GC was not clarified.

As DNA repair pathways, the BER pathway, which possibly handles the largest number of cytotoxic and mutagenic base lesions, has been associated with risk of various types of cancer (26). It corrects DNA modifications such as oxidation, deamination and ring fragmentation that arise either from attack by chemicals or spontaneously (27). Among BER genes, the human apurinic/apyrimidinic endonuclease *APE1* gene is located on chromosome 14q11.2–q12 and consists of five exons spanning 2.21 kb. APE1 produces normal 3'-hydroxyl nucleotide termini by hydrolyzing 3'-blocking fragments from oxidized and alkylated DNA, which are necessary for DNA repair synthesis and ligation at single- or double-strand breaks (28, 29).

Table III. *Association of HOGG1 gene polymorphisms with clinicopathological features of gastric cancers.*

HOGG1 genotypes	Ser/SerN (%)	Ser/Cys+Cys/Cys N (%)	OR #	95% CI	*p*-Value
Grade					
Grade I-2 (n=18)	6 (33.3)	12 (66.7)	7.65	1.63-35.79	0.007
Grade III (n=22)	17 (77.3)	5 (22.7)			
Metastasis					
Yes (15)	12 (80)	3 (20)	6.5	1.17-35.83	0.02
No (25)	4 (16) 15.4	21 (84)			

Association between the *APE1* polymorphism and GC has not been investigated previously. We investigated the association of the most extensively studied Asp148Glu polymorphism of *APE1* and GC risk. Our study is the first report showing an association between the Asp/Glu genotype and Glu allele of *APE1* gene variants and increased risk of GC in a Turkish population. Prior to our study, it was reported that the G allele of *APE1* was associated with an increased mitotic delay after exposure to ionizing radiation (22). The Asp148Glu of *APE1* polymorphism is the only known common non-synonymous *APE1* coding region variant. Functional studies on this polymorphism have shown that the G allele encodes a protein which may have altered endonuclease and DNA-binding activity and reduced ability to communicate with other BER proteins (30). In a small study on X-ray exposure of lymphocytes and effects of polymorphisms of DNA repair genes on chromosome aberrations, samples from individuals with the TG or GG genotype showed higher levels of damage with respect to all the studied measures, including aberrant cells, chromatid breaks, chromatid exchanges, deletions and dicentrics (31). Consistent with these observations our results support the findings of a meta-analysis on *APE1* polymorphism and cancer risk which showed that carrying at least one G allele was associated with a higher cancer risk than carrying the TT genotype (32).

For *HOGG1*, our result indicating no association of Ser326Cys *HOGG1* polymorphism with GC risk is in agreement with those found in Polish, Japanese, Brazilian and Spanish populations (15, 33-35). The lack of association between the *HOGG1* gene polymorphism and GC risk are consistent in these different ethnic study groups, suggesting that enviromental factors are not at play. On the other hand, it was reported that some individual differences, such as drinking and nutritional habits, might alter the association between *HOGG1* polymorphism and the development of GC (36).

In our study, *XRCC1* polymorphism was not associated with an increased risk of GC. Our results are in accordance with no association found between the *XRCC1* Arg399Gln genotypes and GC risk in Korean (17), Chinese (37), and Brazilian populations (38), and in a recent meta-analysis (39). On the other hand, an association was found between the *XRCC1* Arg399Gln variant and reduced risk of cardiac GC in a Chinese population (16). We also found no association between the *XRCC3* gene polymorphism and GC risk. Our result is in agreement with those found in Italian (19), Brazilian (38), Chinese (40) and Polish (41) populations.

In this study, we also did not find any association of either *XPD* or *XPG* polymorphisms with GC risk. In concordance with our results, *XPD* polymorphism did not have independent effects on GC risk (19, 41); however, it might modify smoking- and probably diet-related risks for GC (41). Moreover, *XPD* polymorphism is thought to be an important marker in the prediction of clinical outcome ofchemo-radiotherapy in resected GC patients (42).

For the *XPG* polymorphism, no association was found for GC risk in our study. As yet, there has been no report investigating the association of *XPG* polymorphism and GC risk. More recently, moderate incidence (6.3%) of the frame shift mutation of exon 13 of *XPD* was detected in GC with microsatellite instability (43).

In conclusion, our data show the *APE1* gene polymorphisms appears to play a role in the development of GC. Furthermore, the *HOGG1* genotype seems to be associated with poor histological grade and metastasis in GC. Our findings suggest that DNA repair gene polymorphism is important in the development of GC, as well as relevant to overlapping pathologic features of GC such as grading and staging in this Turkish population. Investigations with larger study groups will elucidate the exact role of DNA repair genes in GC development and progress.

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