RESEARCH COMMUNICATION

Genotype-phenotype Relationship between DNA Repair Gene Genetic Polymorphisms and DNA Repair Capacity

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Abstract

Genotype-phenotype relationships between genetic polymorphisms of DNA repair genes and DNA repair capacity were evaluated in a case-control study of breast cancer. Selected DNA repair genes included were those involved in double-strand break repair (ATM, XRCC2, XRCC4, XRCC6, LIG4, RAD51, RAD52), base excision repair (LIG1), nucleotide excision repair (ERCC1), and mismatch repair (hMLH1). The subjects consisted of histologically confirmed breast cancer cases (n=132) and controls (n=75) with no present or previous history of cancer. Seventeen single nucleotide polymorphisms of 10 genes (ATM -5144A>T, IVS21+1049T>C, IVS33-55T>C, IVS34+60G>A, and 3393T>G, XRCC2 31479G/A, XRCC4 921G/T, XRCC6 1796G/T, LIG4 1977T/C, RAD51 135G/C, 172G/T, RAD52 2259C/T, LIG1 583A/C, ERCC1 8092A/C, 354C/T, hMLH1 5' region -93G/A, 655A/G) were determined by TaqMan assay (ATM) or MALDI-TOF (all other genes). DNA repair capacity was measured by a host cell reactivation assay of repair of ultraviolet damage. The DNA repair capacity (%) did not differ between cases (median 37.2, interquartile range: 23.6-59.6) and controls (median 32.7, interquartile range: 26.7-53.2). However, DNA repair capacity significantly differed by the genotypes of ATM and RAD51 genes among cancer-free controls. Our findings suggest that DNA repair capacity might be influenced by genetic polymorphisms of DNA damage response genes and DNA repair genes.

Key Words: DNA repair - genetic polymorphisms - physiological influence - breast neoplasms

Asian Pacific J Cancer Prev, **9**, 501-505

Introduction

DNA repair pathways have a critical role for maintaining genomic stability and suppressing mutations (Dixon & Kopras, 2004). DNA repair enzymes continuously monitor chromosomes to correct damage caused by exogenous agents such as ultraviolet (UV) light or cigarette smoke, and endogenous mutagens (Wood et al., 2001). Given the functional relevance of the DNA repair system on carcinogenesis, potential associations between genetic polymorphisms of DNA repair genes and cancer risks have been intensively evaluated (Hung et al., 2005; Manuguerra et al., 2006). However, there is scanty information on the functional significance of these polymorphisms.

The DNA repair capacity (DRC) of individuals could be measured by several different methods. Whereas conventional mutagen sensitivity assays are unable to make distinction between DNA damage and repair, the host cell reactivation (HCR) assay rather directly measures the repair kinetics and provides information on the overall DNA repaired (Berwick & Vineis, 2000).

Previously, Ahn et al. described a HCR assay to measure cellular repair of UV-induced DNA damage using quantitation of firefly luciferase activity as the assay endpoint (Ahn et al., 2004). Several groups of DNA repair genes including the double-strand break (DSB), and nucleotide excision repair (NER) gene are well known to be involved in the repair of UV-induced DNA damage (Yasui & McCready, 1998; Dasika et al., 1999). The importance of DSB repair during breast carcinogenesis is supported by the fact that the familial breast cancer susceptibility genes, BRCA1 and BRCA2, are involved in the homologous recombination pathway for DNA double-strand break (DSB) repair (Narod & Foulkes, 2004).

Here, we evaluated the association between genotypes of DNA repair genes and DRC phenotype to understand the biological relevance of these polymorphisms. We also evaluated the effect of individual's DRC phenotype and breast cancer risk in a hospital-based case-control study in a Korean population.

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Materials and Methods

Study subjects

Included in this study was a subset of participants from the Seoul Breast Cancer Study, a case-control study on the genetic susceptibility and breast cancer risk. Histologically confirmed breast cancer patients admitted to Asan Medical Center from November 2001 to January 2003 were recruited. Patients admitted to the same hospital during the same period, and with no previous and present history of cancer, were eligible as controls for the cancer cases.

Blood collection, isolation of lymphocytes, and cell culture

Each subject donated 8 ml of blood collected in heparinized tubes. The lymphocytes were isolated by Ficoll (Pharmacia Biotech Inc., Piscataway, NJ, USA) gradient centrifugation and suspended in freezing medium containing 50% fetal bovine serum, 40% RPMI 1640 medium (Gibco BRL) and 10% dimethyl sulfoxide (at 10^7 cells/ml), and 2.0 ml aliquots were stored in a -160°C liquid nitrogen tank. They were later thawed in batches for the HCR assays.

DNA repair capacity

DNA molecules were placed on parafilm floating on iced water and irradiated by ultraviolet (UV) light from a germicidal lamp (254 nm, Sankyo Denki Co., Japan) for the indicated doses. The cells were cultured in RPMI 1640 medium (supplemented with 15% Fetal bovine serum, 2 mM L-glutamine, 100 U/ml penicillin G and 100 mg/ml streptomycin (Gibco BRL, Gaithersburg, MD) at 37oC and 5% CO2. The diethylaminoethyl-dextran method (Wei et al., 1993) was used to transfect two aliquots with undamaged pCMVluc and two with pCMVluc damaged with UV. The cultures were then further incubated for 40 h after transfection.

The transfected cells were harvested and lyzed with 50 µl of the Reporter lysis buffer (Promega Corp., Madison, WI) followed by one cycle of freezing and thawing. The assays for firefly luciferase activity were performed in one reaction tube using 20 µl aliquots of cell lysates and 80 µl of luciferase substrate mixture (Qiao et al., 2002a). The luminescent signal from the luciferase reaction was monitored by a single-sample luminometer (LUMI-SCINT, Bioscan). The values shown are averages from three separate assays.

Genotyping

Genetic polymorphisms (XRCC2 31479G/A, XRCC4 921G/T, XRCC6 1796G/T, LIG4 1977T/C, RAD51 135G/C, 172G/T, RAD52 2259C/T, LIG1 583A/C, ERCC1 8092A/C, 354C/T, hMLH1 5' region -93G>A, 655A>G) were determined by matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry. Details for genotyping assay were described previously (Lee et al, 2005a). Five SNPs of ATM gene (-5144A>T, IVS21+1049T>C, IVS33-55T>C, IVS34+60G>A, and 3393T>G) were determined by the 5'-nuclease assay (TaqMan) and detailed procedure was also described elsewhere (Lee et al., 2005b).

Statistical analysis

The Chi-square test was used for comparing demographic characteristics and known breast cancer risk factors. DNA repair capacity was presented as a percentage, which was the ratio of fluorescence produced by luciferase assay for the host cells transfected by UV treated plasmid compared with those cells transfected by untreated plasmid. Since the DRC was not normally distributed, medians and interquartile ranges were presented. The differences of the DRC by case and control groups, age categories, and genotypes were evaluated by Wilcoxon rank sum test or Kruskal-Wallis test according to the number of comparison categories. Trend test for the DRC difference of each SNPs was done by linear regression model using the ordinal number of minor alleles. Statistical analyses were performed with SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA).

ATM haplotypes and diplotypes were estimated from genotype data of a larger subject pool of the Seoul Breast Study, which included 981 breast cancer patients and 1,079 controls, by the Bayesian method using PHASE program available from website: http://stephenslab.uchicago.edu/software.html (Lee et al., 2005b). For current analysis, subjects with DCR (%) values over 100 or less than 0 were excluded (cases = 19, controls =11). Finally, results from 132 breast cancer patients and 75 cancer-free controls were presented.

Results

Included in the final analysis were 132 breast cancer patients and 75 cancer-free controls. There were no differences in the distribution of age, menopausal status,

Table 1. DNA Repair Capacity (%)* by Age Group among Breast Cancer Patients and Controls

	All		Controls		Cases		
Age	n	Median (25th, 75th %)	n	Median (25th, 75th %)	n	Median (25th, 75th %)	p-value*
Total	207	36.2 (24.3, 56.8)	75	32.7 (26.7, 53.2)	132	37.2 (23.6, 59.6)	0.53
<40	41	39.1 (36.1, 69.9)	12	31.7 (25.0, 44.9)	29	41.2 (33.3, 71.5)	0.16
40-50	67	38.5 (27.1, 55.8)	25	34.9 (24.6, 55.4)	42	40.3 (27.5, 58.9)	0.32
50-60	62	31.1 (18.6, 44.4)	21	32.2 (27.0, 44.0)	41	29.6 (18.5, 44.4)	0.52
>60	37	39.7 (24.5, 59.8)	17	39.6 (28.5, 65.6)	20	41.7 (18.6, 48.8)	0.54
p-value**		0.21		0.78		0.12	

DNA repair capacity (%): the ratio of fluorescence produced by luciferase assay for the host cells transfected by UV treated plasmid compared with those cells transfected by untreated plasmid calculated by Wilcoxon rank sum test** calculated by Kruskal-Wallis test

Table 1. DNA Repair Capacity (%)# by Genetic Polymorphisms of DNA Repair Genes Among Controls

Genotypes	n	Median (25th, 75th %)	n	Median (25th, 75th %)	n	Median (25th, 75th %)	p-value*	p-value**
ATM								
-5144A>T		AA		TA		TT		
	17	37.7 (30.1, 55.4)	36	39.7 (28.4, 54.5)	17	28.6 (17.4, 33.4)	0.05	0.03
IVS21+1049T>C		CC		TC		TT		
	27	31.6 (18.9, 43.8)	30	39.7 (26.7, 55.8)	13	37.7 (30.1, 65.9)	0.19	0.04
IVS33-55T>C		CC		TC		TT		
	27	29.8 (18.9, 42.4)	26	41.9 (30.6, 55.8)	17	37.7 (30.1, 55.4)	0.06	0.04
IVS34+60G>A		AA		AG		GG		
	22	29.5 (17.4, 39.8)	31	39.7 (27.1, 56.8)	17	37.7 (30.1, 55.4)	0.03	0.02
3393T>G		TT		TG		GG		
	18	36.3 (30.1, 55.4)	29	39.7 (27.1, 56.8)	23	29.8 (17.4, 42.4)	0.05	0.03
XRCC4								
c.921G>T		GG		GT		TT		
	32	32.1 (20.8, 45.2)	20	35.6 (26.1, 64.5)	6	38.1 (31.7, 61.1)	0.41	0.11
RAD51								
nt135G>C		GG		GC		CC		
	37	39.8 (29.8, 59.8)	10	25.4 (20.6, 31.7)	2	27.5 (27.0, 28.0)	0.04	0.04
nt172G>T		GG		GT		TT		
	42	32.8 (27.6, 56.8)	5	21.0 (9.2, 44.7)	2	29.4 (26.1, 32.6)	0.36	0.17
RAD52								
nt2259C>T		TT		CT		CC		
	17	34.9 (29.3, 60.2)	29	37.7 (20.6, 47.5)	11	30.6 (22.6, 45.3)	0.57	0.42
LIG1								
exon 6 nt551A>C		AA		AC		CC		
	22	32.2 (26.1, 44.0)	16	35.0 (23.2, 57.8)	6	35.2 (28.6, 56.8)	0.89	0.61
ERCC1								
3' UTRc. 8092C>A		CC		AC		AA		
	28	30.9 (21.7, 58.5)	26	39.7 (28.0, 51.1)	3	37.7 (19.1, 43.7)	0.66	0.97
c. 354C>T		CC		CT		TT		
	33	34.9 (27.1, 45.3)	22	33.0 (29.3, 60.2)	2	25.4 (24.6, 26.1)	0.37	0.87
hMLH1								
5' region c.-93G>A		AA		GA		GG		
	20	32.7 (25.1, 52.4)	28	39.7 (27.5, 53.5)	9	30.1 (24.6, 34.9)	0.59	0.42
exon8 Ile219Val (A>G)		AA		GA/GG				
	51	32.7 (22.6, 55.4)	2	31.9 (31.7, 32.2)			0.89	

#DNA repair capacity (%): the ratio of fluorescence produced by luciferase assay for host cells transfected by UV treated plasmids compared with untreated plasmids, * calculated by Kruskal-Wallis test, ** calculated by linear regression model using the number of minor allele

body mass index (BMI) and smoking status. However, breast cancer patients were more likely to have family history of cancer among the first and second-degree relatives (7.6%) compared to control group (1.3%) (data now shown).

Overall, there was no difference in the DRC between breast cancer patients (median 37.2, interquartile range: 23.6-59.6) and controls (median 32.7, interquartile range: 26.7-53.2) (Table 1). The DRC of each age group also did not differ among neither cases nor controls. Cases with family history of cancer showed slightly higher DRC (median 60.0, interquartile range: 29.2-84.5) compared to cases with no family history of cancer (median 37.1, interquartile range: 23.3-57.9), however, the difference was not statistically significant (p = 0.15).

We compared the DRC by genotypes of DNA repair genes (Table 2). The XRCC2 31479G>A, XRCC6 61796 G>T, and LIG4 1997 T>C were not polymorphic in our study population. The DRC was significantly different among controls by five genetic polymorphisms of ATM gene. Controls with heterozygous -5144A>T, IVS21+1049T>C, IVS33-55T>C, IVS34+60G>A and 3393T>G polymorphisms of ATM gene showed the highest DRC, and homozygous of major alleles of these polymorphisms showed the lowest DRC. Among other double strand break repair genes, significant difference of the DRC was observed by RAD51 nt135G>C polymorphisms. The DRC was the lowest among subjects with heterozygous alleles and the highest among subjects with homozygous major alleles, and the difference was statistically significant in control group (p = 0.04). No difference of the DRC by genotypes of XRCC4 c.921G>T, RAD51 nt172G>T, or RAD52 nt2259c>T was observed. We did not find associations of the DRC with genetic polymorphisms of base excision repair gene (LIG1 nt551A>C), nucleotide excision repair gene (ERCC1 3' UTRc. 8092C>A and ERCC1 c.354C>T), and mismatch repair gene (hMLH1 5' region c.-93G>A and hMLH1 Ile219Val).

Since all five polymorphisms of ATM gene showed significant difference in the DRC, we compared the DRC by the ATM haplotypes (Figure 1). Control subjects who possessed TCCAG/TCCAG haplotype pair had the lowest DRC. Statistically significant differences of DRC by haplotype pairs, however, did not observed due to small sample size for each haplotype pair strata.

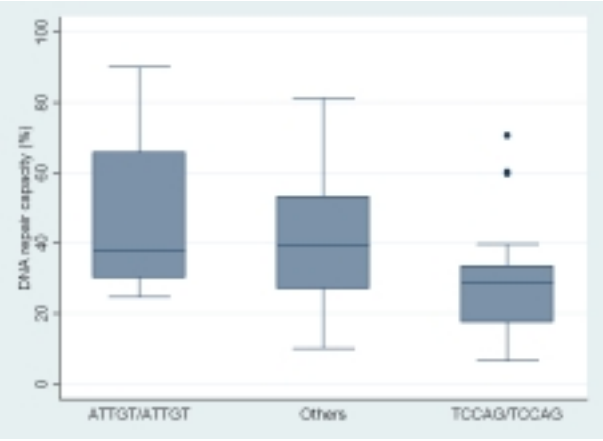

Figure 1. DNA repair capacity (%) by Haplotype Pairs‡ of the Ataxia Telangiectasia Mutated (ATM) Gene among Controls. ‡composed of five polymorphic sites: -5144A>T, IVS21+1049T>C, IVS33-55T>C, IVS+60G>A, and 3393T>G

Discussion

It has been suggested that compromised innate DRC of individuals may be related with a high risk for cancer. Several studies compared the DRC among cancer patients and controls in a case-control design. In a systematic review by Berwick and Vineis, 7 out of 8 studies using host cell reactivation assay showed statistically significant decrease of DRC among patients with basal cell carcinoma of skin, lung cancer, or head and neck cancer (Berwick & Vineis, 2000). After this systematic review published, more evidences for relation between the reduced DRC and breast cancer risk were added (Muller-Vogt et al., 2003; Kennedy et al., 2005; Bau et al., 2007). Kennedy et al. measured DRC from lymphoblastoid cells treated with benzo[apyrene diolepoxide in breast cancer patients/sisters discordant pairs (Kennedy et al., 2005). Mean percent DRC was lower in breast cancer patients and adjusted odds ratios of breast cancer was 2.99 (95% CI 1.45 to 6.17) for the highest quartile of DRC compared to the lowest quartile as the reference (Kennedy et al., 2005).

Recently, Bau et al. demonstrated that low in vivo and in vitro DNA end-joining (EJ) capacities to repair DNA double strand breaks were associated with breast cancer risk (Bau et al., 2007). The in vitro EJ capacity below the median of control group was related with a 3-fold increase in the risk of breast cancer (OR 2.98, 95% CI 1.64-5.43) (Bau et al., 2007). Müller-Vogt et al. evaluated the DRC by microgel electrophoresis in a group of 19 young patients with multiple solid cancer events which occurred at age of initial affliction below 45 years, and a positive family history of malignant disease (Muller-Vogt et al., 2003). Lymphocytes isolated from cancer patients had lower DRC compared those isolated from the controls patients (81.3% vs. 95.3%, $p<0.01$) (Muller-Vogt et al., 2003). We did not find any association between the DRC and breast cancer risk in our study population. Almost every study regarding the DRC and cancer risk was a case-control design. However, cancer burden might either suppress or enhance the DRC of lymphocyte through high metabolic rate and excessive endogenously generated oxidative stress (Berwick & Vineis, 2000). Therefore a cohort study would be an ideal study design to get a definitive conclusion for the relationship between DRC and cancer risk.

In this study, we demonstrated that the DRC of UV-damaged DNA might be modulated by genetic polymorphisms of genes involved in double strand break repair genes, such as ATM and RAD51. Our findings are supported by our previous report for the association of genetic polymorphisms of ATM gene and breast cancer risk (Lee et al., 2005b), although we did not find any association between the DRC and breast cancer risk in the current study. In our previous report, we found that the ATM IVS21+1049 C, IVS34+60 A, and 3393 G allele were associated with an increased risk of breast cancer, and the ATTGT haplotype was associated with decreased breast cancer risk after adjusting for other risk factors for breast cancer (Lee et al., 2005b). Control subjects with the risk genotypes showed the lowest DRC in the current study. Also the TCCAG/TCCAG haplotype pair, which was assigned to the subjects who possessed homozygous for risk alleles for all five SNPs, showed the lowest DRC. It has been reported that ATM is phosphorylated and activated in an ATR-dependent manner following UV lesions and subsequently, ATM and ATR can contribute to UV-induced G2/M checkpoint arrest (Stiff et al., 2006). During arrest, UV lesions may be repaired. Therefore, ATM signaling may be involved in repair of UV lesions. Thus, correlation between low DRC and SNPs of ATM gene in breast cancer may be due to defects in ATM signaling.

The RAD51 family of genes have a critical role in homologous recombination pathway in human cells (Thacker, 2005) and have relevance in breast carcinogenesis with their interaction with BRCA genes (Venkitaraman, 2004). The homozygous CC genotype of 135G>C polymorphism has been associated with 3.18-fold increase in the risk of breast cancer among BRCA2 mutation carriers (Antoniou et al., 2007). We found that subjects with C alleles had the lowest DRC, which could explain the functional significance of the RAD51 polymorphism. Thus, the RAD51 protein may be involved in repair of UV-induced damage, suggesting that variants in the RAD51 gene may modulate genetic predisposition to breast cancer.

Most study investigated the correlation between DNA repair genotypes and phenotypes have targeted nucleotide excision repair (NER) genes, such as XPA, XPC, XPG (ERCC), XPD (ERCC2), and ERCC1 (Spitz et al., 2001; Qiao et al., 2002a; 2002b; Wu et al., 2003; Shi et al., 2004; Shen et al., 2006). Our data did not show any impact of genetic polymorphism of NER genes on the DRC. Shen et al. did not observe any difference in mean DRC by genotypes of ERCC1 8092A>C polymorphism in a total of 160 breast cancer patients-sister discordant pairs (Shen et al., 2006). They did find that a multivariate conditional logistic model, including three SNPs (XPA 62T>C, XPC Ala499Val, and XPG His1104Asp) and smoking status, only modestly predicted DRC after adjusting for case-control status and age of blood donation (Shen et al., 2006). Similarly, Shi et al. observed variation of DRC by the

XPD genotypes only in the controls rather than in the cases, suggesting genetic variants of other DNA repair genes may be involved in these breast cancer patients (Shi et al., 2004).

Age, smoking habits, sex, dietary habits, sunlight exposure, and exposure to pro-oxidants have been proposed as potential confounders for the association between genetic polymorphisms and some DNA damage/repair assays (Berwick & Vineis, 2000). However, we did not find an effect of age or smoking habit on the DRC either among breast cancer patients or controls (data not shown). Radiation therapy or chemotherapy for cancer patients may affect the DRC, therefore including cancer patients who received neo-adjuvant treatment may introduce a bias due to treatment. However, only subjects who did not receive any treatment at the time of recruitment were eligible for our study to minimize the effect of treatment on the DRC.

Limitations of this study include limited test reliability information. Since the inter- and intra-individual variations of HCR assay are relatively large, bigger study sample size are needed to detect a meaningful difference in the DRC phenotype among individuals with different DNA repair genotypes.

In summary, our results revealed a correlation between DNA repair genotypes of double-strand break genes and DRC phenotype. Our previous report on the association between genetic polymorphisms of ATM gene and breast cancer risk could be explained by the effect of genetic polymorphisms on variation of DRC.

Acknowledgements

This study was supported by a grant from the National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea (0620410–1).

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