

# XRCC4 Codon 247\*A and XRCC4 Promoter –1394\*T Related Genotypes but not XRCC4 Intron 3 Gene Polymorphism Are Associated With Higher Susceptibility for Endometriosis

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**ABSTRACT** DNA repair systems act to maintain genome integrity in the face of replication errors, environmental insults, and the cumulative effects of age. Genetic variants in DNA repair genes such as X-ray repair cross-complementing group 4 (XRCC4) might influence the ability to repair damaged DNA. Herein we aimed to investigate whether some XRCC4-related polymorphisms were associated with endometriosis susceptibility. Women were divided: (1) severe endometriosis (rAFS stage IV, n = 136) and (2) nonendometriosis groups (n = 112). The polymorphisms of XRCC4 codon 247, XRCC4 promoter –1394, and XRCC4 intron 3 insertion/deletion (I/D) polymorphism were amplified by PCR and detected by electrophoresis after restriction enzyme (Bbs I, Hinc II) digestions. Genotypes and allelic frequencies in both groups were compared. We observed that XRCC4 codon 247\*A and XRCC4 promoter –1394\*T related genotypes, but not XRCC4 intron 3 I/D polymorphism, are associated with higher susceptibility for endometriosis. Distributions of XRCC4 codon 247\*C homozygote/heterozygote/A homozygote, and C/A allele in both groups were: (1) 89/9.5/1.5% and 93.7/6.3%; (2) 97.3/2.7/0%, and 98.7/1.3% ( $P < 0.05$ ). Proportions of XRCC4 promoter –1394\*T homozygote/heterozygote/G homozygote and T/G allele in both groups were: (1) 94.1/5.2/0.7% and 96.7/3.3%, and (2) 79.4/17.9/2.7% and 88.4/11.6% ( $P < 0.005$ ). Proportions of XRCC4\*I homozygote/heterozygote/D homozygote and A/C allele in both groups were: (1) 67.6/30.9/1.5% and 83.2/16.8%, and (2) 70.5/24.1/5.4% and 82.6/17.4% (nondifference). We conclude that XRCC4 codon 247\*A and XRCC4 promoter –1394\*T related genotypes and alleles, but not XRCC4 intron 3 I/D polymorphism, might be associated with endometriosis susceptibilities and pathogenesis. *Mol. Reprod. Dev.* 75: 946–951, 2008. © 2008 Wiley-Liss, Inc.

**Key Words:** endometriosis; gene repair; polymorphism; SNP; XRCC4

## INTRODUCTION

Endometriosis, a complex disease, is associated with genetic changes, defect, and some tumor behaviors such as invasion and distribution. Ectopic endometriosis constitutes the growth of endometrial tissue in a place other than the uterine cavity. Mutant or defected DNA repairing system is essential for the self-defense against tumorigenesis. DNA damage plays a major role in mutagenesis, carcinogenesis, and aging. Some carcinogenic chemicals can form DNA adducts in vivo and thus lead to DNA damage. Repairing DNA damage is critical for cell proliferation and prevention of cell malformations.

The cell's susceptibility to mutagens and its ability to repair DNA lesions are important for cancer induction, promotion, and progression. Endometriosis displays some features of malignancy, including local invasion and aggressive spread to distant organs. Endometriosis involves a complex interaction or compromise between cell metaplasia, genetic defect, DNA repair, cell stability, and angiogenesis (Vigano et al., 1998; Goumenou et al., 2000; Ferrero et al., 2006). Furthermore, some ovarian tumors, such as endometrioid carcinoma or clear cell carcinoma, are associated to endometriosis (Ali-Fehmi et al., 2006). Since endometriosis is a kind of metaplasia and some features of tumorigenesis, it is logical to suspect some genetic variants of DNA repair gene might contribute to endometriosis pathogenesis. Genetic variations in DNA-repairing genes might be correlated with the pathogenesis of endometriosis. Genetic polymorphisms

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of DNA repair genes might determine the DNA repair capacity (Qiao et al., 2002), which further affect the susceptibilities of endometriosis.

The integrity of damaged DNAs is typically restored as a consequence of the action of certain DNA-repairing enzymes. DNA-repairing gene variations might influence genomic instability as well as impacting protein function, growth intervention and increasing cancer risk. The mutagens' sensitivity and efficacy of DNA repair are affected by variation in several genes, including X-ray repair cross-complementing (XRCC) genes. XRCC is a base-excision repair protein that plays a central role in the repair of DNA base damage and strand breaks. XRCC coordinates the activities of DNA polymerase and ligase for base excision repair (BER) of oxidative DNA damage. XRCC is also a negative regulator of apoptosis (Bu et al., 2006). XRCC group 4 (XRCC4) has been reported to be associated with DNA double strand breaks repairing system. In addition, XRCC4-related genetic variations might play an important biomarker of susceptibility in endometriosis.

Single nucleotide polymorphism (SNP) results from a base substitution mutation. SNPs in protein-coding regions might result in a missense mutation (synonymous), with a change of amino acids or a nonsense mutation (nonsynonymous) occurring in a termination codon. In addition, SNPs in promoter regions can result in reduced or increased gene expression, whereas SNPs in introns can result in defective splicing or a change in transcription rate if a regulatory element is mutated. SNPs occur on average every 1.9 kb in the genome where 1.42 million SNPs have been mapped with over 60,000 being represented within exons and untranslated regions (Marth et al., 2001). SNPs provide a new way for the identification of complex gene-associated diseases such as endometriosis.

Current molecular research mainly focused on steroid hormone receptors and hormone metabolism and their role in endometriosis. The roles and molecular bases of DNA-repair genes upon endometriosis development remain obscure. Notwithstanding, some deficiencies in cellular repair capacity, hidden as SNP, will cause accumulating of genetic deficient, which may lead to carcinogenesis, such as endometriosis. Despite the recent identification of XRCC4 gene polymorphisms, little is known about their phenotypic significance upon endometriosis. Reviewing MEDLINE database, no investigator demonstrated the correlation of XRCC4 gene polymorphisms with endometriosis. In this study, we aimed to evaluate whether XRCC4 codon 247, promoter -1394 and intron 3 insertion/deletion (I/D) gene polymorphisms are attractive markers for predicting the susceptibility of endometriosis. To the best of our knowledge, this is the first survey in this field.

#### PATIENT AND METHODS

Premenopausal Taiwanese women with surgically and histologically diagnosed endometriosis were included.

All patients were divided into two groups: (1) severe endometriosis (stage IV, Revised American Fertility Society classification of endometriosis, 1985) (n = 136) and (2) nonendometriosis group (n = 112). The non-endometriosis statuses were confirmed during the cesarean section or diagnostic laparoscopy. All operations were performed by two surgeons (Y.Y. Hsieh, C.C. Chang). All women accepted the peripheral blood sampling for genotype analyses. The experiment was approved by Ethical Committee and Institutional Review Board of China Medical University Hospital.

The genomic DNA was prepared from peripheral blood leukocytes by use of a genomic DNA isolation kit (Blossom, Taipei, Taiwan). A total of 50 ng genomic DNA was mixed with 20 pmol of each polymerase chain reaction (PCR) primer in a total volume of 25  $\mu$ l containing 10 mM Tris-HCl pH 8.3, 50 mM potassium chloride, 2.0 mM magnesium chloride, 0.2 mM each deoxyribonucleotide triphosphate, and 1 U DNA polymerase (Amplitag; Perkin-Elmer, Foster City, CA). The PCR conditions for XRCC4 gene polymorphisms were designed by ourselves (D.-T. Bau). The PCR primer sequences and condition of each primer were listed in Table 1. The PCR amplification was performed in a programmable thermal cycler GenAmp PCR system 2400 (Perkin Elmer Applied Biosystems, Foster City, CA).

After PCR amplification, the XRCC4 codon 247 and XRCC4 promoter -1394 gene polymorphisms were analyzed by restriction digestion with restriction enzymes (BBS I, Hinc II, New England Biolabs, Inc., Beverly, MA). The XRCC4 intron 3 I/D polymorphisms were determined by the different size of PCR products after electrophoreses. Electrophoresis of the PCR product was performed on a 3% agarose gel and stained with ethidium bromide to visualize the amplified DNA bands. The individual PCR conditions, following electrophoresis and base pairs for their wild and SNP types were listed in Table 1.

Genotypes and allelic frequencies for XRCC4 codon 247, XRCC4 promoter -1394, and XRCC4 intron 3 gene polymorphisms in both groups were compared. Correlations of these gene polymorphisms and endometriosis were evaluated. Allelic frequencies are expressed as a percentage of the total number of alleles. The SAS package (Version 8.1, SAS Institute, Inc., Cary, NC) with  $\chi^2$  and Fisher's exact tests were utilized for statistical analyses. A *P*-value of <0.05 was considered statistically significant.

#### RESULTS

Genotype proportions of different gene polymorphisms of XRCC4 codon 247 and promoter -1394 in both groups were significantly different (Tables 2 and 3). Distributions of XRCC4 codon 247\*C homozygote/heterozygote/A homozygote and C/A allele in both groups were: (1) 89/9.5/1.5% and 93.7/6.3%; (2) 97.3/2.7/0% and 98.7/1.3%, respectively (*P*-value < 0.05, Table 2). Proportions of XRCC4 promoter -1394\*T homozygote/heterozygote/G homozygote and T/G allele in both groups

**TABLE 1. The Primer Sequences, Polymerase Chain Reaction (PCR) and Restriction Fragment Length Polymorphism (RFLP) Conditions for XRCC4 Codon 247, XRCC4 Promoter -1394 and XRCC4 Intron 3 Gene Polymorphisms**

Polymorphisms	Primers sequences (5' → 3') <sup>a</sup>	Denature (°C/sec)	Annealing (°C/sec)	Extension (°C/sec)	Restriction enzyme (°C/min)	SNP sequence	Allelic variants	DNA fragment size (bp)
XRCC4 codon 247 (rs3734091)	F: GCTAATGAGTTGCTGCATTTTA R: TTCTAGGGAAACTGCAATCTGT	94/30	55/30	72/30	BBS I (37°C/60 min)	A C	Ser Ala	204 + 104 308
XRCC4 promoter -1394 (rs6869366)	F: GATCGGAATCAAGATACTGA R: TGTAAGGCCAGTACTCAAACIT				Hinc II (37°C/60 min)	G T		100 + 200 300
XRCC4 intron 3 (rs28860071)	F: TCCTGTACCATTTCAGTGTAT R: CACCTGTGTTCAATTCAGCIT				—	—	Insertion Deletion	139 109

<sup>a</sup>F and R indicate forward and reverse primers.

were: (1) 94.1/5.2/0.7% and 96.7/3.3%; (2) 79.4/17.9/2.7% and 88.4/11.6%, respectively ( $P$ -value < 0.005, Table 3). XRCC4 codon 247\*A and XRCC4 promoter -1394\*T related genotypes are associated with higher susceptibility for endometriosis. Most individuals in both groups appear the wild-related genotype and allele.

In contrast, genotype proportions and allele frequencies of XRCC4 intron 3 I/D gene polymorphism in both groups were nonstatistically different (Table 4). Proportions of XRCC4\*I homozygote/heterozygote/D homozygote and I/D allele in both groups were: (1) 67.6/30.9/1.5% and 83.2/16.8%; (2) 70.5/24.1/5.4% and 82.6/17.4%, respectively (nonsignificant difference, Table 4). The wild or mutant variations for XRCC4 intron 3 I/D gene polymorphism were not associated different susceptibilities of endometriosis. These findings suggested some genetic variations within the promoter/exon but not intron area of XRCC4 might be associated with the genetic presentation such as transcription and translations as well as endometriosis phenotypes and susceptibilities.

## DISCUSSION

Humans are exposed to mutagenic and carcinogenic environment. DNA-repair defect are widely documented in cancer cells. Epidemiological studies suggest that DNA repair capability is variable within human populations (Berwick and Vineis, 2000). An important component of differences among individuals is variation in gene coding sequence (Mohrenweiser and Jones, 1998). The repair of DNA damage protects the genome of cells from the insults of cancer causing agents. Genetic variants of DNA repair genes might contribute to tumorigenesis. Individuals with reduced capacity to repair DNA damage might have an increased susceptibility to several types of cancers. Some polymorphisms involved in the repair of alkylating DNA adduct and DNA base damage might be associated with modulating the cancer risks (Jiao et al., 2006).

Growing evidence suggests that tumorigenesis is a multi-step process of genetic alterations for transforming a normal human cell into a malignant derivative (Hanahan and Weinberg, 2000). Cancer developments require a long period of time to accumulate essential genetic defects. Tumorigenesis would be prompted by selective exogenous or endogenous environmental factors (Elledge and Amon, 2002). The ability of a cell to maintain genomic stability through DNA repair mechanisms is essential to prevent tumor initiation and progression.

Endometriosis is a common gynecologic disease, which generally follows a benign course. In contrast, endometriosis also displays features similar to malignancy, requiring cell differentiations, local invasion, and aggressive spread to distant organs. Recently, several studies and molecular data show that endometriosis could be a precursor of sporadic endometrioid and clear cell carcinomas at extrauterine loci (Prowse et al., 2006). Endometriosis and atypical endometriosis might act as precursor lesions that have the potential to progress into ovarian adenocarcinoma (Ali-Fehmi et al., 2006).

**TABLE 2. Genotypes and Allelic Frequencies for XRCC4 Codon 247 Gene Polymorphism in Women With and Without Endometriosis**

XRCC4 codon 247	Endometriosis, n = 136	Controls, n = 112	P-value <sup>a</sup>
Genotype			0.036
CC	121 (89%)	109 (97.3%)	
AC	13 (9.5%)	3 (2.7%)	
AA	2 (1.5%)	0	
Allelic frequency			0.024
Allele C	255 (93.7%)	221 (98.7%)	
Allele A	14 (6.3%)	3 (1.3%)	

<sup>a</sup>Fisher’s exact tests.

Metaplasia is often observed in ovarian endometriosis and is associated with malignant ovarian epithelial tumor or atypia (Fukunaga and Ushigome, 1998). The metaplasia of endometrial tissue is essential for the establishment and growth of ectopic endometriotic lesions. Deficient DNA-self-repairing or defense process against peritoneal/ovarian metaplastic cells or retrograde endometrial cells during menstruation might be involved with the pathophysiology of endometriosis. Some mutation or aberrance within the ectopic endometrium lesion as well as surrounding peritoneum or ovaries might further promote the ectopic endometrium adhesion and invasion (Renner et al., 2006).

DNA repair systems act to maintain genome integrity in the face of replication errors, environmental insults, and the cumulative effects of age. Identification of genetic variations responsible for reduced DNA repair capacity might allow a better elucidation of the related pathogenesis of endometriosis. Among these DNA-repair genes, XRCC plays an important role in the excision or repair of both damaged bases and single-strand breaks of DNA after chemical or other carcinogen exposure (Jiao et al., 2006; Li et al., 2006). XRCC protein might interact with DNA ligase in recognition and rejoining of DNA strand breaks (Qu and Morimoto, 2005). XRCC is essential for the excision or repair of both damaged bases and single-strand breaks of DNA after chemical or other carcinogen exposure (Li et al., 2006). Cells lacking the XRCC-related activity are hypersensitive to DNA damage. Genetic variations in DNA repair genes, such as XRCC4, might lead to inter-individual variation in DNA repair capacity and modify the associations between exogenous and endogenous carcinogens and endometriosis risk.

XRCC plays a pivotal role in BER by bringing together DNA polymerase β, DNA ligase III, and PARP at the site of DNA damage (Nash et al., 1997; Masson et al., 1998). XRCC-related BER system might targets endogenous DNA damage through induced hydrolysis, oxidative stress, and alkylation, as well as adducts and fragmented bases caused by exogenous agents such as ionizing radiation and alkylating or oxidative agents (Seeberg et al., 1995; Lindahl et al., 1997; Lindahl and Wood, 1999). XRCC may participate in the removal of DNA adducts, the repair of oxidative DNA damage, and the repair of DNA damage attributable to ionizing or oxidative agents (Wilson and Thompson, 1997; Oliver et al., 1999). Compromised XRCC proteins as well as some nucleotide sequence alterations for XRCC family were identified to be associated with individual disorders. XRCC mutations might result in a severe reduction in the level of XRCC protein and in the cellular capacity to repair DNA damage (Zdzienicka et al., 1992). Some mutations might destabilize XRCC through improper protein folding or through disruption of XRCC-specific complex formation (Shen et al., 1998).

XRCC4 is a member of the DNA repair gene family. DNA-repairing-related SNPs might be directly or indirectly correlated with the proliferations of ectopic endometrial cells. Electronic search of publications on the MEDLINE/PubMed database revealed that scanty literatures about XRCC4 genetic variations have been reported. Most literatures about XRCC family presented the distributions of XRCC1–3 genetic variations in individual disorders. There were some associations of XRCC4 polymorphisms with numerous disorders, including breast cancer [XRCC4 X1–3 intron (rs1478485, rs13180316, rs963248), XRCC4 X4 G307T

**TABLE 3. Genotypes and Allelic Frequencies for XRCC4 Promoter –1394 Gene Polymorphism in Women With and Without Endometriosis**

XRCC4-promoter –1394	Endometriosis, n = 136	Controls, n = 112	P-value <sup>a</sup>
Genotype			0.002
TT	128 (94.1%)	89 (79.4%)	
TG	7 (5.2%)	20 (17.9%)	
GG	1 (0.7%)	3 (2.7%)	
Allelic frequency			0.0003
Allele T	263 (96.7%)	198 (88.4%)	
Allele G	9 (3.3%)	26 (11.6%)	

<sup>a</sup>χ<sup>2</sup> test.



**TABLE 4. Genotypes and Allelic Frequencies for XRCC4 Intron3 Insertion/Deletion (I/D) Gene Polymorphism in Women With and Without Endometriosis**

XRCC4-intron3	Endometriosis, n = 136	Controls, n = 112	P-value <sup>a</sup>
Genotype			NS
II	92 (67.6%)	79 (70.5%)	
ID	42 (30.9%)	27 (24.1%)	
DD	2 (1.5%)	6 (5.4%)	
Allelic frequency			NS
Allele I	226 (83.2%)	185 (82.6%)	
Allele D	46 (16.8%)	39 (17.4%)	

<sup>a</sup> $\chi^2$  test.

(rs1056503)] (Allen-Brady et al., 2006), chromosome aberration (XRCC4 I134T; Wilding et al., 2005), lung cancer (XRCC4 I137T; Rudd et al., 2006), etc.

In contrast, the nonsignificant associations of some XRCC4-related polymorphisms with individual disorders have been demonstrated, including breast cancer (XRCC4 921G > T) (Lee et al., 2005) (XRCC4 intron 7 A > G) (Garcia-Closas et al., 2006), somatic mutations (XRCC4 codon 401 Ile/Thr.) (Relton et al., 2004), benzene-induced hematotoxicity (XRCC4 Ala247Ser, Ser307Ser, intron 7 G > A) (Shen et al., 2006), etc. There was only one literature mentioning about XRCC4 Ala247Ser polymorphism (Shen et al., 2006). Furthermore, no investigators demonstrated the roles of XRCC4 promoter -1394 and intron 3 in the individual disorders as well as endometriosis.

In this study, we firstly observed some association existed between endometriosis susceptibility and XRCC4 genetic variations (XRCC4 codon 247\*A and XRCC4 promoter -1394\*T related genotype and allele). These two functional variants might directly or indirectly influence the mRNA translations for XRCC4. The XRCC4 codon 247 genetic variation might result in the synonymous coding change. Therefore, it is plausible to suspect the intervention, modification, determination, or involvement of these two SNPs upon the expression or stability of the XRCC4. Furthermore, there are also predictive effects for these individual polymorphisms upon protein sequence. We also observed the noncorrelations of endometriosis with the XRCC4 intron 3 I/D polymorphism. This intervening sequence located on mRNA-untranslated region might not influence the amino acid coding, mRNA production, genetic expression and illness susceptibilities.

To the best of our knowledge, this is the first study to address the issue of an interaction between XRCC4 genetic variations and endometriosis risk. It suggested some DNA repair gene, such as XRCC4 polymorphisms, might be associated with endometriosis risk as well as playing potential candidate genetic markers in predicting the susceptibility of endometriosis. There is biological plausibility for an association between the XRCC4 polymorphisms in the exon or promoter regions and endometriosis risk. Our study should permit a more precise evaluation of the risks associated with individual susceptibility genes and a better insight into endometriosis pathogenesis. These polymorphisms

might have a potential influence on the expression of this repair protein.

Taken together, XRCC4 codon 247\*A and XRCC4 promoter -1394\*T related genotypes, but not XRCC4 intron 3 I/D polymorphism, might be correlated with endometriosis development and pathogenesis. These findings highlighted the values and potentials of the DNA-repair and XRCC-related genes upon the future surveys of endometriosis. Both XRCC4 codon 247 and XRCC4 promoter -1394 polymorphisms might become potential markers for the prediction of endometriosis susceptibility. It also provides a valuable insight into the pathogenesis of endometriosis. However, the real roles and relationship of this genetic trait upon endometriosis remains complex to be clarified, especially concerning the effects of hormone or life styles additions. Additional in vitro or in vivo researches are requested, including functional studies correlating genotype and phenotype for specific XRCC4 alleles within endometriosis tissue. After the clarification of these issues, some DNA-repairing genetic variations might become useful markers to predict the future development of endometriosis as well as the modulating or interfering factors of related pathogenesis.

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