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DNA Repair Gene (XPD, XRCC4, and XRCC1) Polymorphisms in Patients with Endometrial Hyperplasia: A Pilot Study

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Background: In this study, we aimed to evaluate the association between endometrial hyperplasia and DNA repair gene (XPD, XRCC4, and XRCC1) polymorphisms.

Material/Methods: There were 114 cases enrolled in the study in 4 groups: simple endometrial hyperplasia (SH) (Group 1), complex endometrial hyperplasia without atypia (CH) (Group 2), complex atypical endometrial hyperplasia (CAH) (Group 3), and normal endometrium (NE) (Group 4). Of these cases, 37 cases had SH, 36 cases had CH, 16 cases had CAH, and 25 cases had NE. To evaluate an association between atypia and DNA repair genes, we consider a group that included both SH and CH, the endometrial hyperplasia without atypia cases (Group 5). Genomic DNA was isolated from paraffin-embedded endometrial tissue collected from the Pathology Department of Gaziantep University Medical School. Polymerase chain reaction (PCR) and/or restriction fragment length polymorphism (RFLP) method was used for evaluating of XPD (-751), XRCC4 (-1394 and a variable number of tandem repeats in intron 3), and XRCC1 (-399) genes.

Results: We observed a notable distinction in patients having endometrial hyperplasia without atypia (the SH+CH group) and the CAH group in terms of XPD (-751) gene polymorphisms. A notable contrast was observed in patients with endometrial hyperplasia without atypia (the SH+CH group) and the NE group in terms of XRCC4 (VNTR intron 3) polymorphisms (P=0.026, P=0.018, respectively).

Conclusions: It was evident the DNA repair gene XPD and XRCC4 polymorphisms had a role in the pathophysiology of endometrial hyperplasia.

MeSH Keywords: DNA Repair • Endometrial Hyperplasia • Genes, vif

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Background

Uterine endometrioid carcinoma is the most common type of endometrial carcinoma that develops from endometrial hyperplasia, and its characterized histopathological endometrial abnormalities include glandular complexity and cytologic atypia, in the setting of unopposed estrogen exposure [1]. DNA repair defects might affect genome-wide genetic instability, which can induce further cancer progression [2]. X-ray repair cross-complementing 1 and 4 (XRCC1 and XRCC4), and xeroderma pigmentosum complementary group D (XPD) are 3 major DNA base excision repair genes that act interactively in DNA repair processes [3]. Polymorphisms of these genes might alter the rate of gene transcription, the stability of the messenger RNA, or protein functions. It is plausible that variations in these genes affect an individual's capacity to repair damaged DNA, and thus induce cancer development in normal or exposed individuals. In the literature, although there have been many molecular studies on endometrial tumorigenesis including DNA repair gene polymorphisms focusing on invasive lesions, only a limited number of publications have evaluated the genetic alterations that occur in endometrial hyperplasia [4].

The primary objective of this study was to assess the association between endometrial hyperplasia and XPD, XRCC4, and XRCC1 gene polymorphisms. As far as we know, this is the first assessment of the association between these DNA repair gene polymorphisms in patients with endometrial hyperplasia taking into account atypia and the complexity in existing English language literature.

Material and Methods

The Ethics Committed for Clinical Research of Gaziantep University approved this retrospective study. Patients were selected from a pool of female patients receiving treatment at the Obstetrics and Gynecology Department of Gaziantep University between January 2001 and December 2010; all study patients had a successive endometrial aspiration biopsy (Pipelle®) or had a hysterectomy because of abnormal uterine bleeding. Serial specimens of normal endometrium (NE), simple endometrial hyperplasia (SH), complex endometrial hyperplasia without atypia (CH), and complex endometrial hyperplasia with atypia (CAH) were obtained from the Pathology Department of Gaziantep University. In total, 114 cases were enrolled in this study. Of these cases, 37 cases had SH (Group 1), 36 cases had CH (Group 2), 16 cases had CAH (Group 3), and 25 cases had NE (Group 4). To evaluate an association between atypia and DNA repair genes, we also include an SH and CH (Group 5) to represented endometrial hyperplasia without atypia cases. The isolation of genomic DNA was performed using paraffin-embedded endometrial tissues collected from the Pathology Department of Gaziantep University Medical School [5]. The polymorphisms of XPD (-751), XRCC4 (-1394 and variable number of tandem repeat in intron 3), and XRCC1 (-399) genes were evaluated. Genotyping was performed by polymerase chain reaction (PCR) and/or restriction fragment length polymorphism (RFLP) [6]. The computation for Hardy-Weinberg equilibrium was performed utilizing the De-Finetti program. A χ^2 test was used for statistical analysis of genotype and allele frequencies in groups.

Results

XPD (-751) A-C genotype and allele frequency of groups are presented in Table 1. A notable distinction was observed in endometrial hyperplasia patients without atypia (SH+CH) (Group 5) and the CAH group (Group 3) for both genotype and allele frequency. A/A homozygotes XPD (-751) gene were significantly more frequent among Group 5 than Group 3 (P=0.026) and C/C homozygotes XPD (-751) gene was significantly more frequent among Group 3 than Group 5 (P=0.026). While the A allele was significantly more frequent in Group 5 than Group 3, and the C allele was significantly more frequent in Group 3 than Group 5 (P=0.036, P=0.013 respectively). The observed genotype counts did not deviate significantly from those expected according to the Hardy-Weinberg equilibrium for XPD gene -751 polymorphisms (P>0.05).

XRCC4 gene variable number of tandem repeats in intron 3 (VNTR intron 3) polymorphism I-D genotype and allele frequency of all groups are presented in Table 2. A notable distinction was observed in endometrial hyperplasia cases without atypia (SH+CH) (Group 5) and NE cases (Group 4). While the I allele was significantly more frequent in Group 5 than Group 4, the D allele was significantly more frequent in Group 4 than Group 5 (P=0.024, P=0.025 respectively). The observed genotype counts were not significant according to the Hardy-Weinberg equilibrium for XRCC4 gene intron 3 VNTR polymorphisms (P>0.05).

We did not observe any noteworthy discrepancy in patients in the SH, CH, CAH, and NE groups in terms of XRCC1 (-399) and XRCC4 (-1394) genotype and allele frequency (data not shown).

Discussion

Endometrial carcinoma is the most common malignant tumor of the female genital organs and classified into 2 histologic subtypes: endometrioid type and non-endometrioid type as exemplified by serous adenocarcinoma [1]. These 2 types of endometrial carcinoma have different molecular genetic changes. In the literature, the mutation of p53 gene has been reported in 90% of non-endometrioid type carcinomas; mutations of

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Table 1. XPD (-751) polymorphisms analysis in specimens of simple hyperplasia (SH) (Group 1), complex hyperplasia without atypia (CH) (Group 2), complex hyperplasia with atypia (CAH) (Group 3), normal endometrium (NE) (Group 4), and endometrial hyperplasia without atypia (SH+CH) (Group 5).

XPD (-751)	SH Group 1 n[a] (%)	CH Group 2 n[b] (%)	CAH Group 3 n[c] (%)	NE Group 4 n[d] (%)	SH+CH Group 5 n[e] (%)	*p*
Genotypes						
AA	20 (54.1)	19 (52.8)	4 (25.0)	13 (52.0)	39 (53.4)	0.026[c–e], NS[anothers]
AC	12 (32.4)	12 (33.3)	7 (43.7)	9 (36.0)	24 (32.9)	NS[all]
CC	5 (13.5)	5 (13.9)	5 (31.3)	3 (12.0)	10 (13.7)	0.026[c–e], NS[anothers]
	37	**36**	**16**	**25**	**73**	
Allelles						
A	52 (70.3)	50 (69.4)	15 (46.9)	35 (70.0)	102 (69.9)	0.036[c–d], 0.013[c–e], NS[anothers]
C	22 (29.7)	22 (30.6)	17 (53.1)	15 (30.0)	44 (30.1)	
HWE p	0.173	0.197	0.626	0.475	0.061	

HWE – Hardy-Weinberg equilibrium.

Table 2. XRCC4 (VNTR intron 3) polymorphisms analysis in simple hyperplasia (SH) (Group 1), complex hyperplasia without atypia (CH) (Group 2), complex hyperplasia with atypia (CAH) (Group 3), normal endometrium (NE) (Group 4), and endometrial hyperplasia without atypia (SH+CH) (Group 5).

XRCC4 (VNTR intron 3)	SH Group 1 n[a] (%)	CH Group 2 n[b] (%)	CAH Group 3 n[c] (%)	NE Group 4 n[d] (%)	SH+CH Group 5 n[e] (%)	*p*
Genotypes						
II	19 (51.4)	18 (50.0)	5 (31.3)	6 (24.0)	37 (50.7)	0.018[b–d], NS[anothers]
ID	13 (35.1)	17 (47.2)	8 (50.0)	15 (60.0)	30 (41.1)	0.033[d–e], 0.028[a–d], NS[anothers]
DD	5 (13.5)	1 (2.8)	3 (18.7)	4 (16.0)	6 (8.2)	0.018[b–d], NS[anothers]
	37	**36**	**16**	**25**	**73**	
Allelles						
I	51 (68.9)	53 (73.6)	18 (56.2)	27 (54.0)	104 (71.2)	0.024[b–d], 0.025[d–e], NS[anothers]
D	23 (31.1)	19 (26.4)	14 (43.8)	23 (46.0)	42 (28.8)	
HWE p	0.273	0.196	0.949	0.298	0.981	

HWE – Hardy-Weinberg equilibrium.

PTEN, KRAS, β-catenin, and p53 genes and microsatellite instability have been reported in 5% to 50% of endometrioid-type carcinomas [7]. However, multiple genetic alterations in endometrial tumorigenesis are not clearly understood [8].

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It is known that the most common type of endometrial carcinoma, endometrioid adenocarcinoma, develops from endometrial hyperplasia in the setting of excess estrogen exposure. Epidemiologic studies suggest that the risk of progression to malignancy is low for hyperplasia without atypia, whereas atypia is associated with a significant risk of carcinoma. Despite numerous studies on endometrial tumorigenesis, little is known about the cause of progression from endometrial hyperplasia to carcinoma [9,10].

The XPD protein is a kind of protein that is absolutely necessary for the 5'-3' helicase enzyme to have a role in the DNA repair pathway [11]. Polymorphism -751 in the XPD gene has been associated with a lower DNA repair capacity and a different kind of carcinogenesis [12,13].

A few studies have demonstrated that there is no association between XPD (-751) gene polymorphisms and endometrial cancer, however, in these studies, there was no evaluation of endometrial hyperplasia cases [14,15]. In our study, we observed significant differences in patients with endometrial hyperplasia without atypia (the SH+CH group) and the CAH group. This result suggested to us that the XPD (-751) gene polymorphisms could have a role in the appearance of atypia in endometrial hyperplasia. When AA genotype has a protective role against the appearance of atypia in endometrial hyperplasia, CC genotype could be a predisposing factor for atypia in endometrial hyperplasia.

XRCC4 is generally expressed as a protein (334 amino acids) which plays a role in DNA ligase IV and DNA dependent protein kinase enzyme in the repair of DNA double strand breaks, but its function is unknown [16]. In this study, we evaluated 2 polymorphisms in the XRCC4 gene. This study is the first report on XRCC4 gene polymorphism in endometrial pathology. There have been no studies on the association between endometrial hyperplasia or endometrial carcinoma and XRCC4 gene polymorphism found in the literature.

During our investigation, we noted that patients who had SH or CH and patients in the NE group, in terms of XRCC4 (VNTR intron 3) polymorphisms, showed notable distinctions. These results suggested to us that XRCC4 (VNTR intron 3) gene polymorphisms could have a role on the appearance of endometrial hyperplasia (simple or complex) without atypia. Thus, when DD genotype could have protective role against CH, then II genotype could be a predisposing factor for CH.

The mending of DNA base damage and single-strand DNA breaks is where XRCC1 plays an instrumental part by bringing together a complex of DNA repair proteins including PARP1 and DNA polymerase [17]. Codon 399 is a region that is critical for the role of XRCC1 in single-strand break repair and cell survival [18]. Although there are a few reports about XRCC1 (-399) polymorphisms in endometrial carcinoma, there are no studies on the association between endometrial hyperplasia and XRCC1 gene polymorphism in the English language literature [19,20]. Although Romanowicz-Makowska et al. indicated that XRCC1 A399G polymorphism might be a genetic determinant for developing endometrial cancer [19]. In our study, we observed no association between XRCC1 gene polymorphisms and endometrial hyperplasia including SH, CH, and CAH.

Conclusions

This study demonstrated the correlation of endometrial hyperplasia and variant of XPD, XRCC4 genes. During our investigation, we observed the different steps of endometrial tumorigenesis, including the appearance of endometrial hyperplasia without atypia; once endometrial hyperplasia appeared, progression to atypia was associated with different DNA repair gene polymorphisms. It is evident the DNA repair gene (XPD and XRCC4) polymorphisms have a role in the pathophysiology of endometrial hyperplasia. Nonetheless, a larger study sample, which incorporates endometrial carcinoma studies, will shed more light on this issue.

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