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Original Research

Relationships between vitamin D receptor genetic polymorphisms and endometriosis in Korean women

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Summary

Objectives: Vitamin D and vitamin D receptor (VDR) are closely associated with both various immune system functions and estrogen-related pathways. The authors hypothesized that VDR genetic polymorphisms are associated with endometriosis risk. In this case-control study, the authors investigated the associations between polymorphisms in the VDR gene (*FokI, BsmI, ApaI,* and *TaqI*) and endometriosis risk. *Materials and Methods:* This case-control study included 30 women with endometriosis and 30 women without endometriosis. Genotyping of VDR polymorphisms was conducted using polymerase chain reaction and DNA sequencing. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the association between the four VDR polymorphisms and endometriosis risk using Fisher's exact test. *Results:* The four VDR genetic polymorphisms showed no significant associations with endometriosis risk. Similarly, a combination analysis indicated that no combinations of polymorphisms were associated with endometriosis risk. However, the present analysis combining three polymorphisms revealed very low ORs (CGGT: 0.536, TGTT: 0.250, and CGTT: 0.321). *Conclusion:* The present results suggest that VDR polymorphisms do not affect endometriosis risk in Korean women. However, the genotype frequencies of *ApaI* and *TaqI* differed between endometriosis patients and controls. Therefore, it is necessary to further validate the relationship between VDR polymorphisms and endometriosis risk in large-scale samples. .

Key words: Vitamin D receptor; Polymorphism; Endometriosis.

Introduction

Endometriosis is defined as the existence of endometrial-like (gland and stroma) tissue outside the uterus, and is predominantly detected in women of reproductive age [1]. The symptoms include dysmenorrhea, chronic pelvic pain, deep dyspareunia, and infertility [2, 3]. The suppression of estrogen levels inhibits lesions, whereas the recovery of estrogen levels results in a relapse [4]. Several familial studies have reported that a family history of endometriosis is closely associated with endometriosis risk [5, 6]. Furthermore, chromatid breakage in lymphocytes is associated with the development of endometriosis [7]. This evidence suggests that endometriosis is associated not only with estrogen levels but also with genetic factors. On the other hand, the results of various studies have indicated that natural killer cells, macrophages, and cytokines may be involved in the pathogenesis of endometriosis. This suggests that endometriosis can be considered an autoimmune disorder [8]. Vitamin D plays a role in the regulation of calcium and phosphate transport and in bone mineralization [9]. Furthermore, it is associated with the regulation of cell proliferation, differentiation, and apoptosis [10-12].

Vitamin D regulates the transcription of target genes by binding to vitamin D receptor (VDR), which is involved in diverse systems, including the endocrine system, insulin-like growth factor (IGF) signaling, estrogen-related pathways, and the regulation of vitamin D [13]. Vitamin D and VDR are found in various cells of the immune system. The presence of vitamin D and VDR in peripheral T cells affects the development and function of T cells. Experimental evidence suggests that autoimmune diseases such as inflammatory bowel disease and multiple sclerosis are linked by vitamin D status and VDR signaling [14, 15]. In addition, Liel *et al.* [16] reported that estradiol 17-β (E2) regulates vitamin D activity in osteoblast-like cells. Estrogen increases calcium absorption in women with postmenopausal osteoporosis by increasing serum vitamin D levels [17]. This suggests that vitamin D and VDR are closely associated with various immune system functions and estrogen-related pathways. The VDR gene, located on chromosome 12 (12q14), consists of two promoter regions, six untranslated exon regions (exons 1a–1f), and eight cod-

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Table 1. — *Primer sequences used for polymerase chain reaction amplification and restriction fragment length polymorphisms (RFLPs) of the FokI, BSMI, ApaI, and TaqI polymorphisms of the vitamin D receptor (VDR) gene.*

SNP		Sequence (5'-3')	Tm (°C)	GC (%)	Restriction enzymes	Allele	Fragments (bp)
FokI	F	GGTGGGTGGCACCAAGGATG	61.2	65	*Fok*I	T	31/62/92
	R	GTGAAAGCCAGTGGCTCGGTC	60.8	61.9		C	31/154
BsmI	F	CTGCCCTTAGCTCTGCCTTG	58.2	60	*Bsm*I	G	99/246
	R	CATCACCGACATCATGTCCCC	57.9	57.1		A	345
ApaI (rs7975232)	F	GGAAGGACCTAGGTCTGGATCC	58.3	59.1	*Apa*I	G	161/533
	R	CAGCAACTCCTCATGGCTGAG	58	57.1		T	694
TaqI (rs731236)	F	GTGTTGCCAGGAATGGCCTT	58.5	55	*Taq*I	T	655
	R	CACAAGGGGCGTTAGCTTCATG	58.6	54.5		C	198/457

ing exons (exons 2–9) [18, 19]. Molecular-based epidemiological studies have identified single nucleotide polymorphisms (SNPs) in the VDR gene, including Cdx-2 between exons 1f and 1e, FokI in exon 2, BsmI and ApaI (rs7975232) in intron 8, and TaqI (rs731236) in exon 9 [20, 21]. These polymorphisms may affect VDR function and expression in target cells [22-24]. Based on this evidence, the authors hypothesized that the polymorphisms of the VDR gene are associated with endometriosis risk. In this case-control study, the authors investigated the association between VDR genetic polymorphisms (*FokI, BsmI, ApaI,* and *TaqI*) and endometriosis risk.

Materials and Methods

In this case-control study, the authors enrolled patients undergoing oophorectomy, ovarian cystectomy, or salpingo-oophorectomy at Soonchunhyang University Bucheon Hospital. All women who participated in this case-control study were Korean nationals of Asian descent and were recruited between 2011 and 2013. The Soonchunhyang University Bucheon Hospital Institutional Review Board approved the study. Full informed consent was obtained from the patients prior to the study. Background information on each patient such as age, body weight, height, coexisting diseases, and drug prescriptions was obtained from the hospital information system. The authors collected 60 samples (15 paraffin-embedded tissues and 45 solid tissues) from 30 women with endometriosis and 30 women without endometriosis. For the endometriosis cases, the clinical stages of endometriosis were assessed according to the revised American Fertility Society classification system, and were graded as minimal (Stage I), mild (Stage II), moderate (Stage III), and severe (Stage IV).

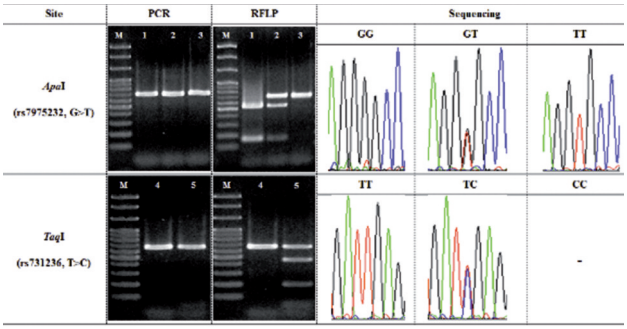
Genomic DNA was isolated from paraffin-embedded tissues and solid tissues.

For paraffin-embedded tissues, a small section (about 20 mg) was placed in a 1.5-mL tube and 1,000 µL of xylene was added, then the tube was vortexed for 30 seconds. All mixtures were centrifuged at 12,000 × *g* for five minutes at room temperature. The supernatant was removed by pipetting, and 1,000 µL of ethanol was added to the pellet to remove residual xylene. The mixtures were then centrifuged at 13,000 × *g* for five minute at room temperature.

The ethanol was carefully removed by pipetting, and then the tubes were dried at 37°C for 15 minute. Solid tissues were homogenized to powder in liquid nitrogen using a clean pestle, and then the powdered tissues were transferred to fresh 1.5-mL tubes using a clean spatula.

Lysis buffer (400 µL, 50 mM Tris-HCl, pH 8.0, 50 mM EDTA, pH 8.0, and 100 mM NaCl) and 40 µL of proteinase K were added to the tissues. The tubes were incubated at 60°C until all tissue

Table 2. — *Representative RFLPs and sequencing results for the VDR genetic polymorphisms.*



M: 100 bp DNA ladder, lane 1: GG allele of ApaI, lane 2: GT allele of ApaI, lane 3: TT allele of ApaI, lane 4: TT allele of TaqI, lane 5: TC allele of TaqI. The GG allele of ApaI is identified by the presence of a 161 bp and 533 bp bands and the TT allele of ApaI by the presence of a 694 bp band. The TT allele of TaqI is identified by the presence of a 655 bp band and the CC allele of TaqI by the presence of a 198 bp and 457 bp bands.

fragments were completely dissolved. Phenol-chloroform isoamyl alcohol (440 µL) was added, and the mixtures were centrifuged at 12,000 × *g* for five minute at room temperature. The supernatants were then transferred to fresh 1.5-mL tubes by pipetting, and 30 µL of 2 M sodium acetate and 900 µL of cold 100% ethanol were added and the tubes were incubated at −20°C for 30 minutes. The supernatant was discarded, and the pellet was washed with 75% ethanol. The tubes were dried at 50°C for three hour. DNA was eluted with 50 µL of 10 mM Tris-HCl (pH 8.0) and stored at –20°C until it was used for genotyping.

Polymerase chain reaction (PCR) amplification of the four polymorphic sites (*FokI, BsmI, ApaI,* and *TaqI*) was performed in 25-µL reactions consisting of 1 µmol/L of each primer, 1 U of Taq polymerase, 10 mmol dNTPs, and 10× PCR buffer (Table 1). The PCR conditions were 94°C for five minutes followed by 35 cycles of 94°C for 30 seconds, 60°C for 30 seconds, and 72°C for 45 seconds, with a final incubation at 72°C for five minutes. After amplification, we performed DNA sequencing (Table 2).

All statistical analyses were performed using GraphPad InStat. The Chi-squared test was used to determine if the identified study conformed to Hardy-Weinberg equilibrium (HWE) for the genotype distribution in the control group. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the association between the four VDR genetic polymorphisms and endometriosis risk using Fisher's exact test. All *p*-values were considered significant at < 0.05.

Results

The associations between the polymorphisms (*FokI, BsmI, ApaI,* and *TaqI*) of the VDR gene and endometriosis

Table 3. — *Genotype frequencies of the four polymorphisms in women with endometriosis and women without endometriosis.*

*Fok*I (T>C)	Case (n=21)	Control (n=28)	OR (95% CI)	*p*-value	HWE in control
TT	5	6	1		
TC	9	13	0.831 (0.193-3.578)	1.000	
CC	7	9	0.933 (0.199-4.373)	1.000	
T allele	19	25	1		
C allele	23	31	0.976 (0.437-2.182)	1.000	*p*-value: 0.748
*Bsm*I (G>A)	Case (n=21)	Control (n=28)	OR (95% CI)	*p*-value	HWE in control
GG	19	27	1		
GA	2	1	2.842 (0.240-33.66)	0.569	
AA	0	0			
G allele	40	55	1		
A allele	2	1	2.750 (0.241-31.41)	0.575	*p*-value: 0.923
*Apa*I (G>T)	Case (n=30)	Control (n=30)	OR (95% CI)	*p*-value	HWE in control
GG	21	19	1		
GT	I7	7	0.905 (0.268-3.058)	1.000	
TT	2	4	0.452 (0.074-2.758)	0.665	
G allele	49	45	1		
T allele	11	15	0.674 (0.280-1.619)	0.507	*p*-value: 0.038
*Taq*I (T>C)	Case (n=30)	Control (n=30)	OR (95% CI)	*p*-value	HWE in control
TT	27	29	1		
TC	3	1	3.222 (0.316-32.91)	0.612	
CC	0	0			
T allele	57	59	1		
C allele	3	1	3.105 (0.314-30.75)	0.619	*p*-value: 0.926

Statistically significant for $p < 0.05$.

risk are summarized in Table 3. The genotype frequencies of the controls did not deviate from HWE. The present results show that the four polymorphisms were not significantly associated with endometriosis risk. For the FokI polymorphism, the ORs for the TC and CC alleles were 0.831 and 0.933, respectively (95% CI: 0.193, 3.578; 0.199, 4.373; $p = 1.000$; 1.000). For the BsmI polymorphism, the authors did not find the AA (homozygous) allele in cases or controls. The GA allele of the BsmI polymorphism had a high OR. However, the GA allele was not significantly associated with endometriosis risk (OR: 2.842, 95% CI: 0.240, 33.66; $p = 0.569$). Similarly, the authors did not find the CC (homozygous) allele of TaqI in cases or controls. Additionally, the TC allele of the TaqI polymorphism not associated with endometriosis risk (OR: 3.222, 95% CI: 0.316, 32.91; $p = 0.612$). However, they found that the genotype frequencies of the TaqI polymorphism differed between women with endometriosis and controls. The TT/TC/CC ratios in women with endometriosis and without endometriosis were 90/10/0% and 96.7/3.3/0%, respectively. For the ApaI polymorphism, the GT and TT alleles showed no relationship with endometriosis risk. However, the TT (homozygous) allele of the ApaI polymorphism had a very low OR (OR: 0.452, 95% CI: 0.074, 2.758; $p = 0.665$). The proportions of the *Apa*I polymorphism genotypes (GG/GT/TT) in women with endometriosis and without endometriosis were 70.0/23.3/ 6.7% and 63.3/ 23.3/13.3%, respectively. The authors then assessed the associations between combinations of the four polymorphisms (*FokI-BsmI-ApaI-TaqI*) and endometriosis risk (Table 4). The results showed that three combinations had low ORs (CGGT: 0.536; TGTG: 0.250; CGTT: 0.321).

Table 4. — *Combination analyses of the four polymorphisms in women with endometriosis and women without endometriosis.*

Combinations	Case (n=21)	Control (n=28)	OR (95% CI)	*p*-value
T-G-G-T	4	3	1.000	
C-G-G-T	10	14	0.536 (0.098-2.942)	0.671
T-G-T-T	1	3	0.250 (0.017-3.773)	0.546
C-G-T-T	3	7	0.321 (0.043-2.418)	0.350
C-G-T-C	1	0	-	-
C-A-T-C	2	1	1.500 (0.089-25.41)	1.000

Statistically significant for $p < 0.05$.

However, three combinations were not significantly associated with endometriosis risk.

Discussion

SNPs are genetic variants that can occur in both coding sequences (exons) and non-coding sequences (introns). If they occur in regulatory regions, including 5′ untranslated regions (UTRs) or 3′ UTRs, they may affect mRNA expression and mRNA stability. If they occur in coding sequences, SNPs affect amino acid sequences, which may affect protein function [3]. Identifying SNPs associated with disease susceptibility may provide biomarkers for early diagnosis and disease prevention.

Endometriosis is an estrogen-related disease, as the survival and growth of endometriosis tissues is dependent on estrogen levels. In addition, endometriotic implants generate cytokines. Cytokines have been implicated in altering immune system functions, including the activities of T cells, natural killer cells, and B cells [25]. Many epidemiological studies have investigated the associations between polymorphisms of numerous genes related to the pathophysiology of endometriosis and endometrio-

sis risk. In particular, many researchers have investigated the relationship between polymorphisms in estrogen receptor genes and endometriosis risk. Among these studies, several reports have suggested that polymorphisms in estrogen receptor genes were highly associated with endometriosis risk [17, 26-29]. However, this finding is not consistent with those from other studies [30-33]. Similarly, the associations between polymorphisms in interleukin genes and endometriosis risk have been investigated. Interleukins are a group of cytokines. The activity of the immune system depends in a large part on interleukins, and they are also associated with autoimmune diseases. Furthermore, several studies have reported that serum interleukin-10 levels were significantly elevated in endometriosis patients [34, 35], and epidemiological studies indicated that interleukin-10 genetic polymorphisms were associated with endometriosis risk [36, 37]. However, not all previous studies produced corroborative results. Vitamin D is associated with estradiol responses and various immune system functions. Furthermore, vitamin D is associated with autoimmune disease [38]. Based on these observations, Vilarino *et al.* [39] examined the relationship between four polymorphisms of the VDR gene and endometriosis risk in Brazilian women. Their results suggested that the four VDR polymorphisms were not associated with endometriosis risk in Brazilian women. Ultimately, the associations between the polymorphisms of many different genes and endometriosis risk have been investigated, but the relationships between polymorphisms and endometriosis risk remain unclear. In this case-control study, the authors investigated four genetic poly- morphisms of VDR and endometriosis risk in Korean women. The present authors' conclusion is that there were no significant associations between the four VDR polymorphisms and endometriosis risk in Korean women. However, they found that the genotype frequencies differed between women with endometriosis and those without endometriosis (TT allele of *ApaI* and TC allele of *TaqI*). There are two limitations in this case-control study. The first limitation is the relatively small sample size of cases and controls. This limitation decreased the statistical power to determine the association between two VDR polymorphisms and endometriosis risk. Second, this case-control study did not consider gene-environment interaction factors such as vitamin D levels, menstrual status, age, smoking status, alcohol status, and disease stage, which may alter the associations between VDR polymorphisms and endometriosis risk. Further analysis with a larger sample size may confirm the relationships between the four polymorphisms (*FokI, BsmI, ApaI*, and *TaqI*) of the VDR gene and endometriosis risk. Additionally, the authors evaluated the associations between other VDR polymorphisms and endometriosis risk in Korean women.

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