Association of intercellular adhesion molecule-1 K469E polymorphism with preeclampsia in Korean population

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<ABSTRACT>

Association of intercellular adhesion molecule-1 K469E polymorphism with preeclampsia in Korean population

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Objective: Endothelial dysfunction is considered to be central in the pathogenesis of preeclampsia. An excessive maternal systemic inflammatory response to pregnancy has been proposed to be responsible for endothelial dysfunction. The ICAM-1 molecule is functionally involved in the regulation of adhesion of leukocytes to the endothelium as well as leukocyte migration, in other words, that expression could stimulate maternal immunological recognition and rejection reactions, and result in disrupted trophoblast trafficking and thereby cause incomplete placentation leading to preeclampsia. In this case-control study, we will examine whether the distribution of genotypic and allelic frequencies of ICAM-1 K469 of Korean women with preeclampsia are

different from those of control group.

Materials and Methods: The ICAM-1 K469E polymorphism was genotyped using sequencing analysis in 42 women with preeclampsia and 138 normotensive controls who had delivered at least two normal term babies. Genomic DNA was extracted from whole blood sample. After gene amplification by PCR and purification, direct sequencing reaction method was used to detect a single nucleotide polymorphism.

Results: The distribution of genotype frequencies and the frequency of the K469 allele of the preeclampsia group were not significantly different from those of the controls. (KK/KE/EE (%) control 45.7/44.2/10.1 vs preeclampsia 59.5/23.8/16.7, $p>0.05$), (K allele (%) control 67.8 vs preeclampsia 71.4, $p= 0.62$) A similar trend was observed between the severe preeclampsia patients and the controls. (KK/KE/EE (%) control 45.7/44.2/10.1 vs severe preeclampsia 59.3/29.6/11.1, $p=0.36$), (K allele (%) control 67.8 vs severe preeclampsia 74.1, $p= 0.45$)

Conclusions: The frequencies of the KK genotype and the K allele were higher in the preeclampsia group than those in the control group. However, there was no statistically significant difference.

Key words : Intercellular adhesion molecule, Polymorphism, Preeclampsia

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I. INTRODUCTION

Preeclampsia is a condition unique to human pregnancy. Occurring in 5-7% of pregnancies, it is the major cause of maternal and perinatal morbidity and mortality, but the pathogenesis of this disorder has not been clearly established. Recently, an excessive maternal systemic inflammatory response to pregnancy has been proposed to be responsible for endothelial dysfunction leading to cellular activation and damage.[1,2] Endothelial dysfunction is considered to be central in the pathogenesis of preeclampsia.[3,4] The inflammatory process is the adhesion of leukocytes to endothelial cells followed by transmigration of these cells into perivascular tissue. Leukocyte endothelial adhesion is governed largely by the interaction of adhesion molecules and their ligands on these cells.

ICAM-1 is a member of the immmunoglobulin superfamily that mediates its functional activity through binding to leukocyte 2-integrins.[5] The ICAM-1 molecule is functionally involved in the regulation of adhesion of leukocytes to the endothelium as well as leukocyte migration.[6] and aberrant ICAM-1 expression was reported in pregnancy disorders that are associated with poor invasion of extravillous cytotrophoblast into maternal spiral arteries, such as preeclampsia.[7,8,9] Many studies have shown that preeclampsia is largely under genetic control, but genetic mechanisms underlying the disorder have yet to be determined.[10,11,12,13,14] The ICAM-1 gene, located in chromosome-19p 13.3-13.2, has at least two biallelic polymorphisms in its coding region. One encoding Arg/Gly is located at codon 241 (R241G) and the other encoding Lys/Glu at codon 469 (K469E). Several inflammatory and autoimmune diseases have been found to be associated with ICAM-1 polymorphisms, including multiple sclerosis[15], inflammatory bowel disease[16], chronic renal allograft failure[17], transplant-associated vasculopathy after cardiac transplantation[18], Behcet's disease[19] and polymyalgia rheumatica/giant cell arthritis[20]. An increased frequency of the ICAM-1 469 EE genotype has been documented in Japanese patients with endometriosis and in Korean patients with spontaneous preterm delivery.[21,22] However, there have been no reports on the association between preeclampsia and ICAM polymorphisms. Based on previous reports, ICAM-1 polymorphisms appear to show different racial distributions. Other studies

involving Korean populations have not found evidence of a genetic polymorphism at codon 241.[23, 24] This finding contrasts with results reported in European populations, including British, Italian, and Spanish populations.[17, 25] Interestingly, studies on the Japanese have also found no evidence of a polymorphism at this site.[26] Therefore, our present study included only the K469E polymorphism. Based on the putative role of ICAM-1 in the inflammation followed by endothelial cell dysfunction and pathogenesis of preeclampsia, we supposed that ICAM-1 K469E polymorphism could be associated with preeclampsia development.

II. MATERIALS AND METHODS

1. Study population

In this study, 42 patients with preeclampsia and 138 control subjects were enrolled at the Department of Obstetrics and Gynecology of Konkuk University Hospital between June 2005 and January 2008. Preeclampsia was defined as hypertension (systolic blood pressure ≥140mmHg and diastolic blood pressure ≥90 mmHg after 20 weeks' gestation) and proteinuria (≥300 mg in a 24 hr urine collection or one dipstick measurement of ≥1+) according to the criteria of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.[27] Severe preeclampsia was diagnosed on the basis of diastolic blood pressure ≥110 mmHg or significant proteinuria (dipstick measurement of ≥2+) or the presence of severity evidences such as headache, visual disturbances, upper abdominal pain, oliguria, convulsion, elevated serum creatinine, thrombocytopenia, marked liver enzyme elevation, and pulmonary edema. The control group consisted of 138 normotensive healthy pregnant women with at least two term deliveries and no history of preeclmapsia. Cases complicated by chronic hypertension, diabetes, chronic renal disease and autoimmune disorders were not included in the study. All women participating in this study, both patients and controls, were of Korean ethnicity.

2. Genotyping of the ICAM gene polymorphism

Genomic DNA was extracted from whole blood using the SolGent genomic DNA prep Kit (SolGent, Korea). We analyzed ICAM K469E polymorphism by direct sequencing method.

A. PCR Amplification

The presence of the K469E polymorphism was determined by PCR amplification with the primers 5'-ACTGGACGAGAGGGATTGTCC-3' and 3'-CCTCAGCACGTACCTCTATAAC-5'. A volume of 25 μL was used for each PCR reaction, which contained 20pM of each primer, 200 μM of each dNTP (desoxyribonucleotide triphosphate), 0.5X Band Doctor™ (SolGent, Korea), 1X EF-Tag Buffer and 1.25 U EF-Taq DNA polymerase (SolGent, Korea) with 100ng/μL of genomic DNA. The conditions of amplification were denaturing at 95ºC-2 min, 35 cycles at 95ºC-1 min, 62ºC-40 sec, 72ºC-1 min, and a finally termination at 72ºC-3 min. The amplified fragments were separated on 1.0% agarose gel electrophoresis

B. Purification and sequencing

The purification of amplified fragments was performed by DNA precipitation with 80% ethanol and the pellet was resuspended in 30 μL of distilled water. The purified products were sequenced in a

ABI 3730XL DNA Analyzer (Applied Biosystems, CA, USA), using BigDye® Terminator v3.1 Cycle Sequencing Kits (Applied Biosystems, CA, USA). Sequences were processed and edited in the software 3730 DNA analyzer data collection (version 3.0).

3. Statistical analysis

The clinical and demographic data of the study groups were compared with Student's t-test and the chi-square test. The Hardy-Weinberg's equilibrium for genotype distribution was estimated by the chi-squared test. Differences in genotype distribution and allele frequency between groups were evaluated using the chi-square test. *p*-values less than 0.05 were considered statistically significant. All statistical analyses were performed with SPSS software (version 12.0; SPSS Inc, Chicago, IL).

III. RESULTS

1. Clinical characteristics of patients and controls

Dermographic and clinical data from the studied subjects are given in TABLE 1. There were significant differences in age and parity. In the case group, gestational age at delivery was significantly shorter and birth weight lower.

TABLE 1. Clinical characteristics of patients and controls

Characteristic	PE patients (n=42)	Controls (n=138)	*p*
Age (years)	32.1±5.4	34.7±3.3	0.0055
Primiparas (n (%))	32 (76.2)	0 (0.0)	<0.001
Gestational age at delivery (weeks)	35.6±3.6	38.9±1.2	<0.001
Fetal birth weight (g)	2,437±884	3,273±217	<0.001

Data are presented as mean ± standard deviation for continuous variables and as number(%) for categorical variables.

PE: preeclampsia

2. Genotyping of the ICAM gene polymorphism

A. Genomic DNA extraction

Genomic DNA was isolated from whole blood.

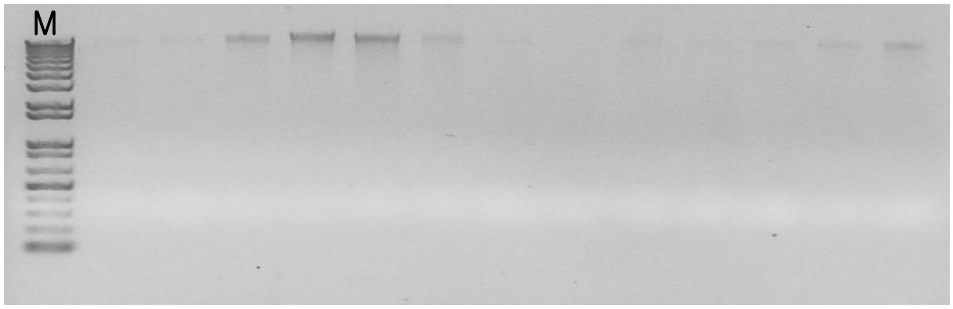

Figure 1. Identification of genomic DNA by PCR

B. PCR amplification

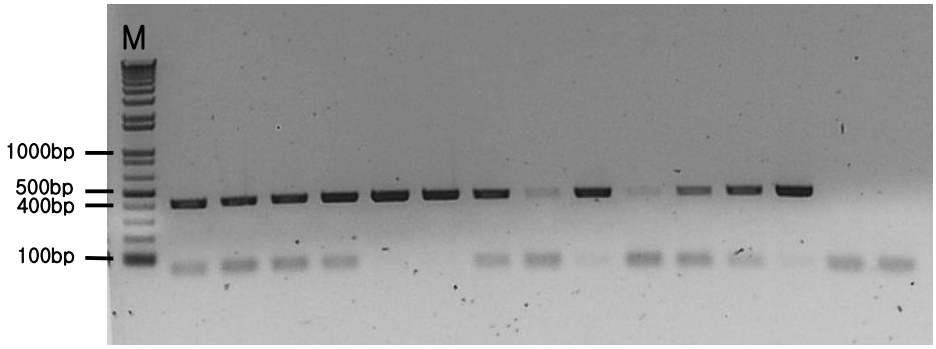

Figure 2. PCR amplification. The amplified fragments were separated on 1.0% agarose gel electrophoresis

C. Purification

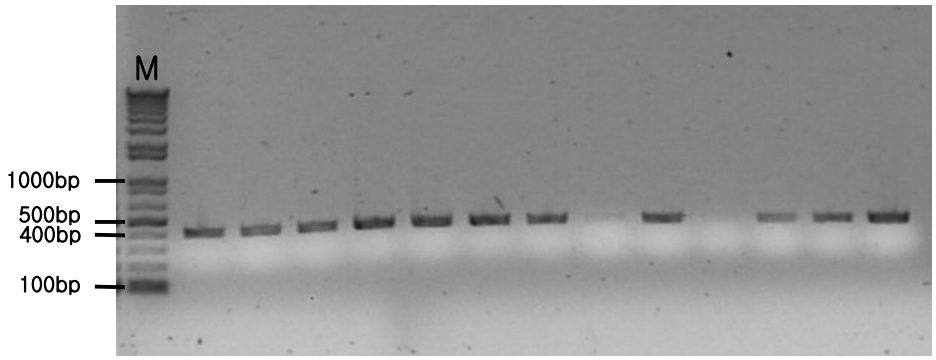

Figure 3. . Purification of amplified fragments. The purification was performed by DNA precipitation with 80% ethanol and the pellet was resuspended in 30 μL of distilled water.

D Sequencing

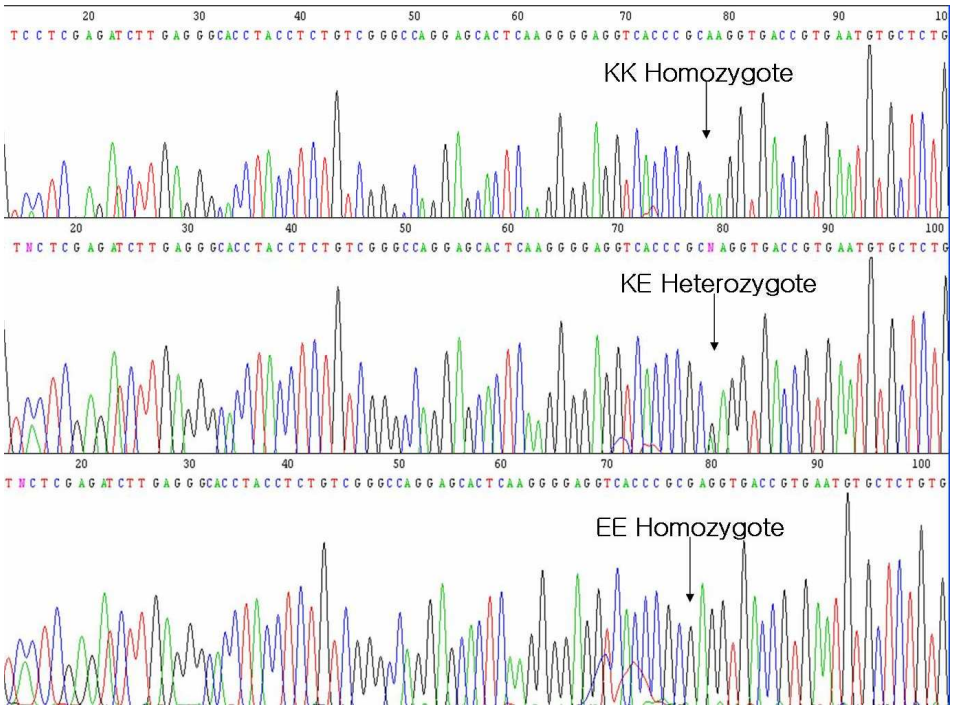

Figure 4. DNA sequencing electropherograms. The ICAM K469E polymorphism was analyzed by direct sequencing method.

3. ICAM-1 K469E polymorphism

A Hardy-Weinberg equilibrium test was performed for the polymorphism and showed that the distribution of the observed genotypes did not differ from the

expected one, in either the patient or the control group. The χ^2 and p values from differences among observed and expected proportions were: case group 4.23, 0.12; control group 0.00, 1.00. The genotype and allele frequencies of the gene polymorphism in the preeclamptic and control groups are displayed in TABLE 2. The allelic frequencies of the case subjects (K 0.71, E 0.29) were not significantly different from those of the control subjects (K 0.68, E 0.32) (p= 0.62).

TABLE 2. Allelic frequencies of the K469E polymorphism among patients and controls

	PE patients (n=42)	**Severe PE (n=27)**	**Control (n=138)**
Allelic frequency (n (%))			
K	60 (71.4)	40 (74.1)	187 (67.8)
E	24 (28.6)	14 (25.9)	89 (32.2)
	P=0.62, χ^2 1.34, df 1	P=0.45, χ^2 0.57, df 1	

PE: preeclampsia

The genotype frequencies of the gene polymorphism in the preeclamptic and control groups are shown in TABLE 3. The genotype distribution of K469E polymorphism was similar between the preeclampsia and the control groups (p > 0.05). There was also no significant association between the control and severe preeclampsia groups in the allelic frequencies and genotype

distributions.

TABLE 3. Genotypic frequencies of the K469E polymorphism among patients and controls

	PE patients (n=42)	Severe PE (n=27)	Control (n=138)
Genotype frequency (n(%))			
KK	25 (59.5)	16 (59.3)	63 (45.7)
KE	10 (23.8)	8 (29.6)	61 (44.2)
EE	7 (16.7)	3 (11.1)	14 (10.1)
	p> 0.05 χ^2 5.84, df 2	P=0.36, χ^2 2.04, df 2	

PE: preeclampsia

There was also no increase in the risk of preeclampsia for that gene under any model of inheritance (Table 4, 5).

TABLE 4. Dominant genotypic frequencies of the K469E polymorphism among patients and controls

	PE patients (n=42)	Severe PE (n=27)	Control (n=138)
Dominant genotypes (n(%))			
KK	25 (59.5)	16 (59.3)	63 (45.7)
KE+EE	17 (40.5)	11 (40.7)	75 (54.3)
	P=0.16, χ^2 1.96, df 1	P=0.28, χ^2 1.17, df 1	

PE: preeclampsia

TABLE 5. Recessive genotypic frequencies of the K469E polymorphism among patients and controls

	PE patients (n=42)	**Severe PE (n=27)**	**Control (n=138)**
Recessive genotypes (n(%))			
KK+KE	35 (83.3)	24 (88.9)	124 (89.6)
EE	7 (16.7)	3 (10.1)	14 (10.4)
	P=0.38, χ^2 0.77, df 1	*P*=0.85, χ^2 0.04, df 1	

PE: preeclampsia

IV. DISCUSSION

The specific factors initiating endothelial damage in preeclampsia are unknown. However, it is interesting that the serum ICAM-1 concentration in patients who subsequently developed preeclampsia was reported to be significantly elevated from early pregnancy to the onset of preeclampsia.[28] Meanwhile, serum ICAM-1 concentration decreased in the early stages of women with normal pregnancies.[29] These findings are consistent with the possibility that abnormal expression of adhesion molecules may be involved in the failure of placentation leading to preeclampsia.[30,31] Furthermore, the recent study suggested that serum from patients with preeclampsia stimulated the expression of ICAM-1 on trophoblasts, of which expression could in turn stimulate maternal immunological recognition and rejection reactions, and result in disrupted trophoblast trafficking and thereby cause incomplete placentation leading to preeclampsia.[32] Functional roles of ICAM polymorphisms were suggested based on the findings that the serum level of ICAM-1 is associated with R241G polymorphism.[33] But the functional relevance of the ICAM-1 K469E polymorphism remains unclear. However, it is interesting to note that the +469 E allele has been shown to be associated with chronic allograft failure in renal transplantation, in which up-regulation of adhesion molecules has also been reported.[17] The above-mentioned findings make this gene a good candidate for association with preeclampsia. However,

these results indicate that K469E polymorphism in ICAM gene does not seem to increase the risk of preeclampsia. We also found that no increase in the risk of preeclampsia for that gene was observed under any model of inheritance. The reason for the lack of association between the ICAM-1 K469E polymorphism and preeclampsia observed in this study remains unclear.

The involvement of the placenta in the pathogenesis of preeclampsia implies a fetal contribution to the development of the disorder. Because trophoblast cells are fetal in origin, this finding raises the possibility that fetal instead of maternal ICAM-1 gene polymorphisms influence the risk of preeclampsia.

The gene polymorphisms of other adhesion molecules, such as P-selectin and E-selectin, were not associated with the risk of preeclampsia.[34] These findings suggest that the gene polymorphisms of the adhesion molecules may not affect the risk of preeclampsia. Since ICAM-1 polymorphisms appear to show different racial distributions, further investigation in other ethnic groups is expected. This is a case-control study with small numbers, not a cohort study. However, to the best of our knowledge, ours is the first study to evaluate the association between the ICAM K469E polymorphism and preeclampsia. So, this finding will need to be confirmed in a large cohort of preeclampsia women.

V. CONCLUSION

Based on the putative role of ICAM-1 in the inflammation followed by endothelial cell dysfunction and pathogenesis of preeclampsia, we supposed that ICAM-1 K469E polymorphism could be associated with preeclampsia development and analyzed that polymorphism by direct sequencing method. The frequencies of the KK genotype and the K allele were higher in the preeclampsia group than those in the control group. However, there was no statistically significant difference. In summary, this study suggests that polymorphism in ICAM-1 genes do not seem to be risk factors for preeclampsia in Korean population.

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< ABSTRACT (IN KOREAN)>

제 1형 세포간부착분자 (Intercellular adhesion molecule-1)의 K469E 유전자 다형성과 전자간증 발생 간의 연관성

< 지도교수 : 박 용 원 >

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권 한 성

목적: 혈관 내피의 기능 부전은 전자간증의 중요한 발병기전이며 이러한 혈관 내피 기능 부전이 발생시키는 원인 중 임신 조직에 대한 모체의 과도한 염증 반응이 연관되어 있다고 알려져 있다. 제 1형 세포간부착분자는 백혈구 등의 염증 관련 세포가 혈관 내피로 이동 및 부착하는데 관여한다. 임신 시에는 혈관 내피뿐만 아니라 영양막세포 등에 과발현하여 모체의 면역학적 인지와 거부 반응을 일으켜 영양막세포가 자궁내 나선 동맥 (spiral artery)로 침습해 들어가는 것을 제한하며 이러한 과정 통해 전자간증을 유발할 수 있다. 제 1형 부착분자의 유전자 다형성은 여러가지 염증 관련 질환과 자가 면역 질환의 발생 위험과 연관성이 있다고 보고되고 있다. 따라서 본 연구에서는 제 1형 세포간부착분자의 유전자 다형성이 한국인의 전자간증 발생과 연관성이 있는지 알아보고자 하였다.

연구대상 및 방법: 42명의 전자간증 산모과 138명의 정상 혈압이며 2

회 이상 정상 만삭 분만을 한 산모를 각각 대상군과 대조군으로 하였고, 유전자 다형성은 직접염기서열분석방법을 이용하였다. 대상군 및 대조군의 유전자형과 대립유전자의 발생 빈도에 차이가 있는지 분석하였다.

결과: 제 1형 세포간부착분자의 K469E 유전자형은 한국인 전자간증군과 대조군 간에 통계학상 유의한 분포의 차이가 없었다. 또한 각 대립유전자의 발생 빈도 역시 두 군간 유의한 차이를 보이지 않았다. (KK/KE/EE (%) 대조군 45.7/44.2/10.1, 전자간증군 59.5/23.8/16.7, p>0.05), (K allele (%) 대조군 67.8 , 전자간증군 71.4, p= 0.62) 이러한 경향은 중증 전자간증 산모를 대상군으로 하였을 경우에도 마찬가지였다. (KK/KE/EE (%) 대조군 45.7/44.2/10.1, 중증 전자간증군 59.3/29.6/11.1, p=0.36), (K allele (%) 대조군 67.8, 중증 전자간증군 74.1, p= 0.45)

결론: 한국인 전자간증군에서 제 1형 세포간부착분자의 K 대립유전자 및 KK 유전자형의 발생 빈도가 대조군에 비해 높았으나 통계학적으로 유의한 연관성은 없었다.

핵심 되는 말 : 제 1형 세포간부착분자, 유전자 다형성, 전자간증