

## 알코올 의존 환자에서의 Aldehyde Dehydrogenase II와 CYP2E1 유전자 다형성과 임상적 특성간의 연관성\*

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### Association of Genetic Polymorphisms of Aldehyde Dehydrogenase II and CYP2E1 and Clinical Characteristics of Patients with Alcohol Dependence \*

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#### ABSTRACT

**O**bjective : This study was to explore the relation of genetic polymorphisms of ALDH2 and CYP2E1 to clinical characteristics of alcoholic patients and alcohol induced liver damage.

**M**ethods : The genotype and allele frequencies of 128 male hospitalized patients who met DSM-criteria for alcohol dependence were compared with 128 healthy male control subjects. The genetic informations of ALDH2 and CYP2E1 were identified with the technique of polymerase chain reaction and restriction fragment length polymorphism. The clinical characteristics of the alcoholic patients were assessed and analyzed in relation to the family history of alcoholism. For the relation of CYP2E1 genetic polymorphism to the liver damage, the blood levels of various liver function indicators such as ALT, AST, and protein were checked out.

**R**esults : 1) The alcoholic patients with the family history of alcoholism had the earlier onset of age ( $p=0.001$ ), the longer duration of illness( $p=0.045$ ), and higher NCA scores( $p=0.018$ ) than those without the family history of alcoholism.

2) Most alcoholic patients were homozygous for ALDH2\*1, compared to control subjects. ( $p=0.000$ )

3) There was no difference of CYP2E1 distribution between alcoholic patients and control subjects. However, alcoholic patients having mutant c2 allele showed higher alcoholism severity scores( $p=0.004$ ) and more hospitalizations( $p=0.014$ ) than those having c1 allele.

4) There was no relationship between CYP2E1 genotype and the functional abnormalities of the liver.

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62

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**Conclusion :** This study suggests that ALDH2\*1 is highly related with alcohol dependence. Also mutant c2 allele of CYP2E1 is correlated with the severity of alcoholism and the number of hospitalization. But genetic polymorphism of CYP2E1 seems to have no relation to liver damages.

**KEY WORDS :** Alcohol dependence · Genetic polymorphism · Aldehyde dehydrogenase · Cytochrome P4502E1.

## 서 론

알코올 의존증은 전 세계적으로 심각한 사회문제가 되고 있다. 알코올 의존증의 발병 원인은 유전적 요인과 환경적 요인이 복합적으로 작용하는 것으로 알려져 있다. 특히 알코올 대사 효소인 알데하이드 탈수소효소(ADH)와 알코올 탈수소효소(ALDH)의 유전적 다형성이 알코올 의존증의 발병과 관련이 있는 것으로 보고되고 있다.

ADH와 ALDH는 알코올을 무해한 물질로 대사시키는 데 중요한 역할을 한다. ADH는 알코올을 아세트알데하이드로 산화시키고, ALDH는 아세트알데하이드를 아세트산으로 산화시킨다. ALDH2\*1은 ALDH2의 활성형으로, 알코올 의존증과 강한 관련성을 보인다. 반면 ALDH2\*2는 비활성형으로, 알코올 의존증 발병 위험을 낮춘다.

CYP2E1은 알코올을 아세트알데하이드로 산화시키는 주요 효소이다. CYP2E1의 c2 대립형질은 c1에 비해 발현량이 높고, 이는 알코올 대사 속도를 증가시켜 알코올 의존증의 심각성과 입원 횟수와 관련이 있다. 그러나 CYP2E1의 유전적 다형성은 간 손상과는 관련이 없는 것으로 나타났다.

본 연구는 알코올 의존증 환자와 일반인 간의 ALDH2\*1, CYP2E1 c2 대립형질의 분포 차이를 조사하고, 알코올 의존증의 심각성과 입원 횟수와의 관련성을 분석하였다. 연구 대상은 1997년 8월 1일부터 1998년 8월 31일까지 DSM-IV 기준을 사용하여 진단된 알코올 의존증 환자 10명과 일반인 31명이었다.

연구 대상 및 방법

1. 연구 대상

1) 환자군

1997년 8월 1일부터 1998년 8월 31일까지 DSM-IV 기준을 사용하여 진단된 알코올 의존증 환자 10명

MAST (Michigan Alcoholism Screening Test) 가 13<sup>21)</sup>

128 가  
 , 가 ,  
 AST, ALT, alkaline phosphatase, bilirubin,  
 protein, albumin  
 (severity) National Council  
 on Alcoholism (NCA) major criteria diagno-  
 stic level 1 NCA<sup>22)</sup>

2) 대조군

가 3  
 1 : 1 (matching) 128  
 .  
 가  
 . 가  
 가

2. 연구 방법

1) DNA 추출

1ml EDTA , DNA  
 - 20 . DNA  
 Wizard Genomic DNA Purification Kit (Promega)  
 . 450 μl 1.35ml  
 가 20  
 , 450 μl 가  
 150 μl 4  
 . 1.5ml tube  
 isopropanol 450 μl 가  
 3  
 70% ethanol 450 μl DNA 3  
 PCR - 20<sup>23)</sup>

2) Polymerase chain reaction-restriction fragment length polymorphism

(1) Aldehyde dehydrogenase ALDH2

primer<sup>23)</sup> Sense primer  
 5' - CCACACTCACAGTTTTCTCTT - 3'  
 , anti-sense primer 5' - AAATTACAGGGT-  
 CAACTGCT - 3' . PCR genomic  
 DNA 1.0 μg, dNTP 800 μM, MgCl2 1.5mM,  
 Tris - HCl 10mM, pH 8.3, Taq polymerase (TaKaRa,  
 Japan) 2.0 unit 25 μl . PCR  
 thermocycler (PTC - 100TM, MJ Research, INC. USA)  
 94 3 denaturation  
 94 1 30 , anealing 50 30 , extension  
 74 30 35 extension  
 74 7 . PCR  
 ethidium bromide 2% agarose gel  
 가 134bp  
 . PCR MboII  
 6 . ethidium  
 bromide 12% polyacrylamide gel  
 eletrophoresis (PAGE) UV transillumi-  
 nator . 134bp band ' D '  
 , 124bp band가 ' N '

(2) Cytochrome P - 450 2E1 CYP2E1

primer<sup>27)</sup> Sense primer  
 5' - CCAGTCGAGTCTACATTGTCA - 3'  
 , anti-sense primer 5' - TTCATTCTGTC-  
 TTCTAACTGGCA - 3' . PCR ge-  
 nomic DNA 1.0 μg, dNTP 800 μM, MgCl2  
 1.5mM, Tris - HCl 10mM, pH 8.3, Taq polymerase  
 (TaKaRa, Japan) 2.0 unit 25 μl  
 . PCR thermocycler (PTC - 100TM, MJ Re-  
 search, INC. USA) 94 5  
 denaturation 94 1 , anealing 53 1  
 , extension 74 30 35 ex-  
 tension 74 7 .

PCR ethidium bromide 43.9 ± 8.4 .  
 2% agarose gel 128 , 가 68  
 가 410bp . PCR (53%) 가 60 (47%)  
 RsaI 6 . 가 . 25.7 ± 8.4  
 ethidium bromide 2% ag- 가 31.5 ± 9.0  
 arose gel UV transilluminator (p=0.001), 가  
 . 410bp band ' c2 ' , 16.5 ± 7.9 , 가 13.5 ± 8.7  
 360bp band가 ' c1 ' . 가 (p=  
 c1 가 , CYP2E1 0.045). NCA 가  
 (c1c1) c1 c2 가 5.6 ± 1.5 가 5.0 ± 1.5  
 , CYP2E1 (c1c2, c2c2) c2 가 NCA  
 . (p=0.018)( 1).

### 3. 자료 분석

chi - square , 가 ,  
 , chi - square  
 t - test . CYP2E1 가  
 CYP2E1 가  
 ANOVA , two - way  
 t - test  
 p<0.05  
 SPSS/PC V7.5

## 결 과

### 1. 환자군의 임상적 특성

128 43.6 ± 7.3 , 가  
 15.1 ± 8.3 , 28.5 ( 2). CYP2E1  
 ± 9.06 , NCA 5.3 ± 1.5 , MAST NCA CYP2E1  
 27.9 ± 7.1 5.0 ± 1.5, CYP2E1

### 2. 알코올 의존 유전자 다형성 빈도

#### 1) Aldehyde dehydrogenase II (ALDH2)

ALDH2 NN 127  
 (99.2%), ND 1 (0.8%), DD 0 (0%)  
 NN 63 (48.4%), ND 54 (43%), DD  
 11 (8.6%) NN  
 가 (by chi - square test, p<0.05).  
 ' N ' ' D ' ,  
 가 253(99.6%) 1(0.4%) ,  
 180(70.3%) 76(29.7%)  
 ' N ' 가 (by chi - squ-  
 are test, p<0.05)( 2).

#### 2) Cytochrome P-450 2E1(CYP2E1)

CYP2E1

**Table 1.** Clinical characteristics according to family history in alcoholic patients(Mean ± SD)

	With Family Hx.(n=68)	Without Family Hx.(n=60)	t	df	p
Mean age(year)	42.4 ± 7.6	45.0 ± 8.0	1.849	126	0.067
Age of onset(year)	25.7 ± 8.4	31.5 ± 9.0	3.567	126	0.001
Duration of illness(year)	16.5 ± 7.9	13.5 ± 8.7	-2.021	126	0.045
Hospitalization(No.)	3.2 ± 2.2	2.5 ± 1.6	-1.971	122	0.051
NCA(score)	5.6 ± 1.5	5.0 ± 1.5	-2.395	126	0.018

analysed by independent t-test

NCA : National Council on Alcoholism

**Table 2.** Genotype and allele frequencies of ALDH2, CYP2E1 gene in alcoholic patients and control subjects (No/%)

ALDH2*	Genotype			Allele	
	NN	ND	DD	N	D
Alcoholics	127/99.2	1/0.8	0/0	253/99.6	1/0.4
Controls	63/48.4	54/43	11/8.6	180/70.3	76/29.7
CYP2E1**	c1c1	c1c2	c2c2	c1	c2
	Alcoholics	79/62.7	40/31.7	7/5.6	198/78.6
Controls	63/54.8	50/43.5	2/1.7	176/76.6	54/23.4

\* : significant difference between alcoholic patients and control subjects by chi-square test, p < 0.05

\*\* : no difference between alcoholic patients and control subjects by chi-square test

**Table 3.** Clinical characteristics according to CYP2E1 gene polymorphism in alcoholic patients (Mean ± SD)

	CYP2E1		F	df	p
	c1 group (n=79)	c2 group (n=47)			
Age of onset (year)	28.9 ± 9.0	27.6 ± 9.1	0.386	1	0.536
Duration of illness (year)	15.3 ± 8.0	15.1 ± 9.1	0.844	1	0.844
Hospitalization (No.)	2.6 ± 1.8	3.5 ± 2.1	6.250	1	0.014
NCA (score)	5.0 ± 1.5	5.8 ± 1.4	8.640	1	0.004
With Family history	41/79 (51.9%)	27/47 (57.4%)			0.583

c1 group : those who had only c1 allele

c2 group : those who had one or two c2 allele

Chi-square test were performed for family history and two-way ANOVA between CYP2E1 group and family history were performed for the others

5.8 ± 1.4 c2 가  
가 (by two - way ANOVA, p < 0.05).  
2.6 ± 1.8, CYP2E1 3.5 ± 2.1  
c2 가  
(by two - way ANOVA, p < 0.05) ( 3).

**3. CYP2E1 유전자형에 따른 간손상의 정도 비교**

c1  
c2 aspartate aminotransferase  
가 60.7 ± 61.6 74.5 ± 69.9, alanine aminotransferase가 34.9 ± 31.9 45.8 ± 40.7, alkaline phosphatase가 94.0 ± 76.3 87.4 ± 48.9 bilirubin  
1.4 ± 0.9 1.4 ± 0.8, protein 7.0 ± 0.8 6.7 ± 0.8, albumin 4.0 ± 0.8 4.0 ± 0.7  
c1, c2

**Table 4.** Blood level of liver function indicator according to CYP2E1 gene polymorphism in alcoholic patients (Mean ± SD)

	c1 group	c2 group
AST	60.7 ± 61.6	74.5 ± 69.9
ALT	34.9 ± 31.9	45.8 ± 40.7
Alkaline phosphatase	94.0 ± 76.3	87.4 ± 48.9
Bilirubin	1.4 ± 0.9	1.4 ± 0.8
Protein	7.0 ± 0.8	6.7 ± 0.8
Albumin	4.0 ± 0.8	4.0 ± 0.7

c1 group : those who had only c1 allele

c2 group : those who had one or two c2 allele

SD : standard deviation

There are no differences by independent Student t-test

24) 가  
2 7  
25) 가

**고 찰**

가 가 가

가 , 가 , 가 <sup>29)</sup> c2  
가 , 가 , 가 c2  
가 , 가 , 가 <sup>30)</sup> c2  
가 , 가 , 가 <sup>31-33)</sup> CYP2E1  
가 가 가  
ALDH2 NN 83.3% CYP2E1  
89.4%, <sup>11)12)</sup> 가 92.9%, 가  
가 가 96.2%<sup>36)</sup> 가 <sup>34)36)</sup>  
99.2% 1 CYP2E1 128  
ALDH2 NN 114 114  
c1c1 51.8%, c1c2 39.5%, c2c2  
ALDH2 8.7%  
ALDH2 <sup>11)12)</sup> 66.3%, 30.6%, 3.06% , <sup>27)</sup> c2  
<sup>27)</sup> 가 가 <sup>29)30)</sup>  
10% DD <sup>4)</sup> <sup>27)31)</sup>  
1.9~5.4%<sup>9)</sup> 가 ,  
Goedde Agarwal<sup>13)</sup> ND DD 가 <sup>35)</sup>  
ALDH가 CYP2E1 inducibility  
가 가 가 CYP2E1  
king region 5' - flan-  
가  
6%  
83% CYP2E1  
가 c2 NCA 가 , 가  
가 가  
CYP2E1 inducibility 가 ,  
가 CYP2E1 ,  
<sup>28)</sup> 가 가 ,  
10 가 <sup>14)</sup> 3~4 , ,  
가 CYP2E1 , c2  
가 가  
National Council on Alcoholism  
severity  
NCA 가

가  
c1, c2

가  
ADH, ALDH2, CYP2E1  
가 , c2 가  
linkage disequilibrium 가  
CYP2E1

27)29)33)

35)

가

가 가

가 가

가

가 가

가 CYP2E1

가

ADH 2, 3

가

중심 단어 : Aldehyde dehydrogenase · Cytochrome P450 2E1.

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