

단가아민 산화제 A CA 반복 유전자 다형성이 한국 알코올의존 남자환자의 행동특성과 임상양상에 미치는 영향

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The Effects of Monoamine Oxidase A CA Repeat Polymorphism on Behavioral Trait and Clinical Characteristics in Korean Male Alcoholics

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ABSTRACT

There are several candidate genes in genetic study of alcoholism. Among them, allelic associations have been reported between MAOA CA repeat polymorphism and alcohol dependence, recently. And also, several studies have been investigated genotype-phenotype relationships between MAOA CA repeat polymorphism and clinical manifestations.

The authors tried to identify differences in allelic frequency of MAOA CA repeat polymorphism between alcohol dependence and controls, and in behavioral trait and clinical characteristics according to MAOA CA repeat polymorphism. We also tried to investigate genotype-phenotype relationships between MAOA CA repeat polymorphism and behavioral trait such as aggression.

We examined 49 male patients with alcohol dependence(DSM-IV) who had been admitted in Yong-In Mental Hospital from June 1st 1998 to October 31th 1998. We performed semistructured interview for demographic and clinical characteristics. Self-report questionnaire for BDHI(Buss-Durkey Hostility Inventory) was given to all subject at least 4weeks later after admission. Using polymerase chain reaction and polyacrylamide gel electrophoresis, MAOA CA repeat polymorphism were observed in 52 male controls and 49 male patients with alcohol dependence. We divided alcoholic patients into two groups according to allelic length of MAOA CA repeat polymorphism ; alcoholics with short alleles(119bp, N=20) and alcoholics with long alleles(123bp, N=29). T-test, χ^2 -test and Fisher exact probability test were used for statistical analysis.

There were no significant differences in frequency of each allele and short and long alleles of MAOA CA repeat polymorphism between alcoholics and controls. But there were significant differences in clinical symptoms and behavioral trait between alcoholics with short and long alleles.

In clinical symptoms, alcoholics with long alleles used alcohol more frequently during one month before admission, had much more maximum amount of beer drinking and reported withdrawal seizure more frequently than with short alleles. In contrary, alcoholics with short alleles expressed depressed mood and guilty feeling more frequently and wanted complete abstinence as a treatment goal more frequently than with long alleles.

In behavioral trait, alcoholics with long alleles had higher total aggression score and showed much more self-assertive attitude(subscale of expression of aggression) than with short alleles. Allelic length of MAOA CA repeat polymorphism was correlated with self-assertive attitude and accounted for 9% of the variance of self-assertive attitude. And also, predictable variables of allelic length of MAOA CA repeat polymorphism were drinking frequency

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and self-assertive attitude.

Our findings suggest that MAOA CA repeat polymorphism may provide some behavior modifying role especially in self-assertive attitude and indirect symptom modifying role in Korean male alcoholics.

KEY WORDS : Alcohol dependence · Monoamine oxidase · Polymorphism.

서 론

가 (complex disease) .

MAOA가 (endogenous neurotransmitter) MAOB (Shih 1993) MAOB MAOA 가 (Brunner 1993a, b) MAOA가

(1997 ; 1995 ; Gade 1998 ; Vanyukov 1995a). , MAOA (coding region) MAOA (candidate gene) (Tivol 1996) MAOA MA - hyde dehydrogenase (1998 ; 1996 ; 1992 ; 1991 ; Chen 1996 ; Higuchi igil Breakefield 1991) MAOA 가 (noncoding region) *MspI* (association) (Hotamisl - 1995 ; Thomasson 1991) 가 dop - amine serotonin (neurotransmitter) , Shih (1993) MAOA CA 가 (1997 ; 1997 ; 1997 ; Noble 1991 ; Blum 1990) . MAOA 가 MAOA (Sabol 1998). MAO(Monoamine Oxidase) (Devor 1994b ; von Knorring 1985 ; Gottfries 1975) MAOA (intron) CA (Murphy Wyatt 1972) (Hsu 가 (Skekim 1982 ; Pandey 1980 ; 1996 ; Vanyukov 1995a ; Parsian 1995) (Va - Sherif 1991). , MAO nyukov 1995a) (Vanyukov 1995b) (Brunner 1993a, b) 가 가 가 MAOA 가 MAOA 가 MAO (Sullivan 1979 ; Major Murphy 1978) , Major Murphy(1978) MAO 가 MAOA CA (marker) 가 MAOA , MAOB MAOA MAOA 가 MAOA 가 MAOA CA MAOA 가 (cloning) MAOA CA

연구 방법

75

1. 연구대상 및 방법

1998 6 1998 10
49
18 65 52
가
2 가 DSM - IV(APA 79 21 0.78 0.
1994)
DSM - IV
4 가, 가
18 65
62
0 3
가 가

3. 실험 방법

1) 혈액 채취 및 DNA 분리

가
DNA (1998)
5ml
heparine - lithium tube
5ml
-20
1.5ml microfuge tube 2 가
15
1ml phosphate - buffered sa -
line(PBS) 15
5% Chelex resin 100 µl
가 , 100 2
3 5 µl (polymerase chain re -
action ; PCR)

2) 연쇄중합반응

, sense primer 5' - AGAGACTAGA -
CAAGTTGCAC - 3' , antisense primer 5' - CACT -
ATCTTGTTAGCTCACT - 3'
. 95 5 (dena -
turation) 95 1 , 58 45 (anne -
aling), 72 50 (extension) 3 cycles
95 1 , 56 45 , 72 50
33 cycles . 10 72

2. 연구도구

1) 공격성척도 : BDHI(Buss-Durkee Hostility Inventory)

7

50mM MgCl₂, 100 pmole, 10mM dNTPs, 10x (160mM(NH₄)₂SO₄, 670mM Tris - HCl(pH 8.8 at 25 °C), 0.5% Tween - 20), 0.2 µg genomic DNA 3 unit, BioTaq™ Taq polymerase 0.5 µl(5 units/1 µl)

6% polyacrylamide gel
110 130 (basepair ; bp)
1x Tris - borate - EDTA(TBE) 100 volt, 20

3) 증폭된 생성물의 분석

Denaturation gel 8M urea, 6% polyacrylamide, sequencing plate plate - meth - acryloxypropyltri - methoxy silane(Sigma) plate Sigmacoat™(Sigma) silver staining

M13mp18 marker . Marker DNA sequencing Ac - cuPower™ sequencing kit(Bioneer)
Innis (1988) 31.0 x 38.5cm denaturation gel(Gibco BRL)
1x TBE buffer 55W constant 2

sequencing plate plate
30 (10% glacial acetic acid)
가 2 3 가 ultrapure water
(1.0g silver nitrate, formaldehyde 1.5ml in 1 liter) 30
. 10 ultrapure water
cold developing (30g sodium carbonate, 200 µl sodium, 1.5ml formaldehyde in 1 liter)
2 가 (1).

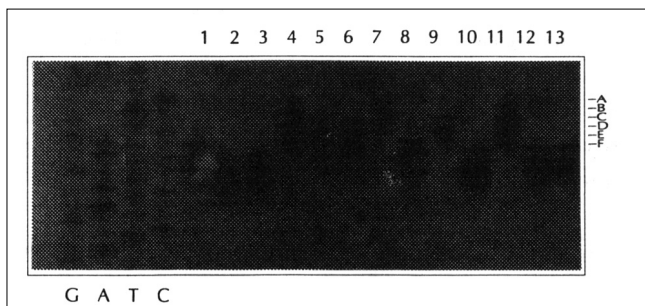


Fig. 1. Electrophoresis band patterns of the subjects by a PCR amplification of the CA repeat polymorphism region in the second intron of the MAOA gene. Allele A : 127bp/Allele B : 125bp ; Lane 4,7,44/Allele C : 123bp ; Lane 5,6,9/Allele D : 121bp/Allele E : 119bp ; Lane 1,8/Allele F : 117bp ; Lane 2, 3,10,12,13

4) 통계처리 및 분석

SPSS/PC⁺ version 7.5
MAOA CA

² - test Fisher exact probability test
MAOA CA
t - test, Fisher exact probability test
MAOA CA (par - tial correlation test)
(MANOVA)
MAOA CA
(stepwise linear regression analysis)
t - test, ² - test, Fisher exact probability test, partial correlation test
p<0.05

결 과

1. 알코올의존 환자군과 대조군에서 MAOA CA 반복 유전자다형성 대립유전자의 빈도

MAOA CA

49 52
² - test 가 (² = 4.998,

Table 1. Allelic frequencies of MAOA CA repeat polymorphism in alcoholic patients and controls

Length of alleles (basepair)	Alcoholics(N=49) N(%)	Controls(N=52) N(%)
117	11(22.4)	13(25.0)
119	9(18.4)	8(15.4)
121	0(0.0)	0(0.0)
123	5(10.2)	12(23.1)
125	22(44.9)	17(32.7)
127	2(4.1)	1(1.9)
129	0(0.0)	1(1.9)

²=4.998, df=5, p=0.416
Two-tailed Fischer exact probability test(²=4.984, p=0.408)
N=Number of individuals

Table 2. Short and long allelic frequencies of MAOA CA repeat polymorphism in alcoholic patients and controls

Length of alleles (basepair)	Alcoholics(N=49) N(%)	Controls(N=52) N(%)
119	20(40.8)	22(42.3)
123	29(59.2)	30(57.7)

²=0.023, df=1, p=0.879

df = 5, p = 0.416), 가 (cell) 5
 가 Monte Carlo
 method Fischer exact probability test
 가 가 ($\chi^2 = 4.984$, p = 0.408)
 (1). ,
 . 121bp가
 , MAOA CA
 가 (bimodal distribution) , 119bp
 가 20 , 22
 123bp 29 , 30
 CA
 가 ,

Table 3. Demographic characteristics according to length of alleles

	alcoholics with short alleles 119bp(N=20) mean±SD	alcoholics with long alleles 123bp(N=29) mean±SD	t	p
Age(years)	43.30 ± 4.93	40.52 ± 4.87	1.955	.057
Education(years)	10.10 ± 2.59	9.86 ± 3.26	.272	.787
	N=20(%)	N=29(%)	χ^2	p
Marital status			6.570	.213
Unmarried	2(10.0)	10(34.5)		
Married	6(30.0)	5(17.2)		
Divorced	8(40.0)	11(37.9)		
Death	0(0.0)	1(3.4)		
Separated	3(15.0)	1(3.4)		
Cohabiting	1(5.0)	1(3.4)		
Religion			1.054	1.000
Catholic	3(15.0)	5(17.2)		
Protestant	7(35.0)	9(31.0)		
Buddhist	1(5.0)	2(6.9)		
Others	0(0.0)	1(3.4)		
No	9(45.0)	12(41.4)		
Occupation			7.926	.273
Managers	1(5.0)	0(0.0)		
Office worker	3(15.0)	4(13.8)		
Salesman	3(15.0)	5(17.2)		
Service	1(5.0)	1(3.4)		
Agriculture	4(20.0)	4(13.8)		
Labourer	2(10.0)	11(37.9)		
Army, police	1(5.0)	0(0.0)		
No	5(25.0)	4(13.8)		
Socioeconomic status			5.074	.260
Low	8(40.0)	4(13.8)		
Low-middle	4(20.0)	11(37.9)		
Middle	6(30.0)	11(37.9)		
Middle-high	1(5.0)	1(3.4)		
High	1(5.0)	2(6.9)		

Two-tailed t-test and Fisher exact probability test

Table 4. Clinical characteristics according to length of alleles

	alcoholics with short alleles 119bp (N=20) mean±SD	alcoholics with long alleles 123bp (N=29) mean±SD	t	p
Age of onset(yrs)	32.85 ± 6.49	30.28 ± 6.86	1.320	.193
Loss of control(yrs)	32.15 ± 6.08	30.59 ± 7.16	.797	.627
Duration of illness (yrs)	9.70 ± 6.32	10.24 ± 5.96	-.305	.762
Amount(bottles)				
Average(soju)	2.55 ± 2.10	2.78 ± 1.66	-.421	.676
Maximum(soju)	5.80 ± 4.02	6.45 ± 3.87	-.567	.573
Average(beer)	1.40 ± 0.73	2.33 ± 2.37	-1.972	.056
Maximum(beer)	5.50 ± 4.73	11.26 ± 7.92	-3.178	.003**
Frequency (days/month)	18.95 ± 7.43	24.72 ± 7.80	-2.597	.013*
Severity	4.45 ± 0.51	4.55 ± 0.57	-.638	.526
	N=20(%)	N=29(%)	χ^2	p
Drinking frequency			13.451	.001**
Several times a year	1(5.0)	0(0.0)		
Several times a month	0(0.0)	0(0.0)		
Several times a week	6(30.0)	1(3.4)		
Almost daily	11(55.0)	13(44.8)		
Everyday	2(10.0)	15(51.7)		
Course			.956	.811
Persistent	17(85.0)	25(86.2)		
Episodic	3(15.0)	3(10.3)		
Unspecified	0(0.0)	1(3.4)		
Tolerance			5.094	.083
Same	3(15.0)	4(13.8)		
Decreased (after increased)	14(70.0)	12(41.4)		
Increased	3(15.0)	13(44.8)		
Seizure			8.137	.032*
Yes	0(0.0)	7(24.1)		
No	20(100.0)	22(75.9)		
Depressive feeling			5.596	.023*
Yes	13(65.0)	9(31.0)		
No	7(35.0)	20(69.0)		
Guilty feeling			8.116	.016*
Yes	19(95.0)	18(62.1)		
No	1(5.0)	11(37.9)		
Family loading			.883	.394
Yes	9(45.0)	17(65.4)		
No	11(55.0)	12(41.4)		
Type			.063	.801
I	9(45.0)	12(41.4)		
II	11(55.0)	17(58.6)		

Table 4. Continued

	alcoholics with short alleles	alcoholics with long alleles	t	p
	119bp (N=20) mean ± SD	123bp (N=29) mean ± SD		
Treatment goal			7.762	.020*
Complete abstinence	16(80.0)	13(44.8)		
Infrequent social drinking	2(10.0)	13(44.8)		
Frequent social drinking	1(5.0)	1(3.4)		
No mistake	1(5.0)	2(6.9)		

Statistically significant by two-tailed t-test and Fisher exact probability test (*p<0.05, **p<0.01)
yrs ; years

Table 5. Comparisons of BDHI between alcoholics with short and long alleles

	alcoholics with short alleles	alcoholics with long alleles	t	p
	119bp (N=20) mean ± SD	123bp (N=29) mean ± SD		
Total aggression	20.90 ± 6.80	24.38 ± 4.92	-2.080	.043*
Control of aggression	4.50 ± 1.99	5.28 ± 2.14	-1.285	.205
Expression of aggression	4.00 ± 1.49	4.90 ± 0.81	-2.714	.009**
Responsive aggression	8.20 ± 3.86	9.48 ± 3.08	-1.292	.203
Spontaneous aggression	4.20 ± 2.61	5.07 ± 1.98	-1.326	.191

BDHI : Buss-Durkee Hostility Inventory
Statistically significant by two-tailed t-test(*p<0.05, **p<0.01)

Table 6. Correlations among each variables in alcoholics

	Length	Total	Control	Expression	Responsive	Spontaneous	Frequency
Total	.1984						
Control	.0962	.3764**					
Expression	.3723**	.4791**	.2501				
Responsive	.1097	.8038**	-.0134	.1999			
Spontaneous	.0959	.6861**	.1207	.1825	.4372*		
Frequency	.3804**	.4036**	.0489	.1512	.3269	.1914	
Amount	.3269*	.0733	.0156	.1257	.0926	.0780	.2118

Two-tailed partial correlation test controlling for age(*p<0.05, **p<0.01)

Length : Length of alleles ; Total : Total aggression ; Control : Control of aggression ; Expression : Expression of aggression ; Responsive : Responsive aggression ; Spontaneous : Spontaneous aggression ; Frequency : Frequency of alcohol drinking(days/month) ; Amount : Maximum amount of beer drinking(bottles)

Table 7. Multivariate analysis of variance of aggression in alcoholics

Dependent variable	r ²	Independent variable	F	p	Eta
Total aggression	.316	Frequency	6.956	.012*	.142
		Age	6.252	.016*	.130
Control of aggression	.258	Age	8.630	.005**	.170
Expression of aggression	.245	Family loading	4.322	.044*	.093
		Length	4.139	.048*	.090
		Subtype	2.764	.104	.062
Responsive aggression	.161	Frequency	4.664	.037*	.100
Spontaneous aggression	.149	Age	3.463	.070	.076

*p<0.05, **p<0.01

119bp 가 (S)
123bp 가 (L)
,
가
($\chi^2 = 0.023, df = 1, p = 0.879$) (2).

2. 알코올 의존 환자에서 MAOA CA 반복 유전자 다형성의 장, 단 대립유전자에 따른 사회인구학적 특성
49 S (20) L (29)

, , , , , ,
가
(3).

3. 알코올 의존 환자에서 MAOA CA 반복 유전자 다형성의 장, 단 대립유전자에 따른 임상양상

MAOA CA
가
Cloninger (1987) 가 ,
가
S 5.50 ± 4.73
L 11.26 ± 7.92 L S
(t = - 3.178, p = 0.003).

, 가 .

Table 8. Stepwise linear regression models for allelic length of MAOA CA repeat polymorphism in alcoholics

Dependent variable	F value	df	Sig F	r ²	Independent variable	Beta	Sig T
Length	15.278	1,47	.000	.245	Drinking frequency	.495	.000
Length	11.836	2,46	.000	.340	Drinking frequency	.447	.001
					Expression of aggression	.311	.014

Length : Allelic length of MAOA CA repeat polymorphism

S 18.95 ± 7.43 10% (7).
 L 24.72 ± 7.80 L S MAOA CA
 (t = -2.597, p=0.013).
 L 가 (²=13.451, p
 =0.001), L (8).
 가 (²=8.137, p=0.032), L S MAOA CA
 가 S 가 MAOA CA
 가 (²=5.596, p=0.023 ; ²=8.116, p=0.
 016). S 가
 (²=7.762, p=0.020)(4).
**4. 알코올의존 환자에서 MAOA CA 반복 유전자다형성의 대
 립유전자에 따른 공격성척도**
 MAOA CA
 가 S 20.90 ±
 6.80 L 24.38 ± 4.92 L S
 (t = -2.080, p=0.043), MAOA CA (association)
 S 4.00 ± 1.49 L 4.90 ± 0.81 L (Hsu 1996 ; Vanyukov 1995a ; Pa -
 S 가 (t = -2.714, p=0.009) rsian 1995)
 (5). Hsu (1996) MAOA CA
 MAOA CA
 가 가 (r = -0.317, p=
 0.026) MAO 가
 (r=0.3723, p<0.01 ; r=0.3804, p<0.01 ;
 r=0.3269, p<0.05)(6).
 MAOA CA L 가 S 가
 , , 가 , , 가
 가
 (p=0.016 ; p=0.012) 13%, 14% , Vanyukov (1995a) MAOA
 가 (p=0.005) CA 가
 17% , 가
 가 (p=0.048 ; p=0.044) 가
 9% . 가
 가 (p=0.037) L S

가 . , MAOA CA OA 가 가 MA -
가 가 OA CA 5 - HIAA 가 가
가 가 가 가 MAOA CA
가 가 Vanyukov (1995b) , 가 ,
MAOA CA 가 ,
, 가 가
, MAOA (var - 가
iable numbers of tandem repeat) , 가
(Samoc -
howiec 1999) . 가 가
가 (Ghodsian - Carpey Baker DSM - IV 가 2
1987) . MA - 가 DSM - IV
OA CA 가 ,
MAOA CA ,
가
, MAOA CA
X
가 가 가
가 purine pyrimidine 가 가
Z - DNA (Co - 가
mings 1998). , MAOA CA
, Z - DNA 가 DNA helix 가
(bases) Hardy - Weinberg equilibrium
가 , Z - DNA (gene regulation) 가
가 (phenotypic effect)
가 (Gade 1998). , Epplen (1996) 가가
(multifactorial disease) (si -
mple repeats) (protein binding) 요 약
(gene expression)
. MAOA CA
가 (Gade 1998 ;
Vanyukov 1995a) 가 MA -
OA CA 가
MAOA CA MAOA S L
가 MAOA CA 가
. 가
MAOA CA MA - , L S

가 . MAOA CA
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 가 가 가
 MAOA CA
 , 가 가
 MAOA 가
 중심 단어 : 가

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