

한국인 알코올 중독 환자에서 도파민 D₂ 수용체의 대립유전자 연합

이강준* · 이민수*[†] · 콧동일*

Allelic Association of the Dopamine D₂ Receptor in Korean Alcoholics

Kang-Joon Lee, M.D.,* Min-Soo Lee, M.D.,*[†] Dong-II Kwak, M.D.*

ABSTRACT

The author attempted to examine the allelic association between the A1 allele of Dopamine D₂ receptor and alcoholism in Koreans. The allelic distribution of Taq I polymorphism of the D₂ dopamine receptor gene with alcoholism was examined in 67 Korean alcoholics and compared with 100 Korean controls. In alcoholics, the numbers of alcoholics with A1A1, A1A2 and A2A2 were 11(16.4%), 30(44.8%) and 26(38.8%) respectively and in controls with A1A1, A1A2 and A2A2 were 17(17.0%), 42(42.0%) and 41(41.0%), respectively. The prevalence of the A1 allele in alcoholics was 61.2% and 59.0% in controls. And the frequency of the A1 allele in alcoholics and controls were 0.39 and 0.38, respectively. There was not significant difference in the frequency of the A1 allele between alcoholics and controls. This data suggest that the A1 allele is not associated with alcoholism in Koreans.

The author conclude that our data do not support an allelic association between the A1 allele at Dopamine D₂ receptor and alcoholism. Further systemized studies will be necessary to determine whether the role of allele of Dopamine D₂ receptor is major effect gene or modifying effect gene in the pathogenesis of alcoholism.

KEY WORDS : Alcoholism · Dopamine D₂ receptor · Allelic association.

서 론

가

4, 6, 11
(association) (linkage)
(Hill 1975, 1988 ; Sigeta 1980).

가 (Am -
merican Psychiatric Association 1987).

가 (American Psychiatric Associ -
ation 1987), 가 , ,
(Cloni - 1978 ; Seeman 1984), 가 (Koob Bloom 1988 ; Lee
1978 ; Seeman 1984), (Blum 1990) 11
q22 - 23 D₂

D₂

Blum (1990) A1
(Clonin -

Department of Neuropsychiatry, College of Medicine, Korea University,
Seoul, Korea

[†] : , 136 - 705 5가 126 - 1 Blum (1990) A1
) (02) 920 - 5354,) (02) 927 - 2836 , (Clonin -

ger 1991 ; Comings 1991 ; Noble 1993)가
 , Bolos (1990) D₂
 , Cook (1992), Gelernter
 (1991), Goldman (1992), Schwab (1991), Turner (1992)
 Bolos (1990) . Parsian
 (1991) 가

A1

D₂

가

(polymerase chain reaction ;

PCR)

D₂

연구 대상 및 방법

1. 연구 대상

DSM - R(APA 1987)
 (alcohol dependence) 67 (27
 70) 가

100

2. 연구 방법

1) Genomic DNA의 추출 및 정제

1.5ml 13,000rpm 1
 (pellet) ACE shocking (NH₄Cl
 8g, Na₂EDTAH₂O 1g, KH₂PO₄ 0.1g 1L
) 500 μl 3
 2
 pellet 400 μl nuclei ly -

sis [Tris(pH 8.0) 10mM, NaCl 400mM, EDTA 2mM]
 pellet 10% SDS 27 μl pro -
 teinase K 10 μl 가 56 2
 NaCl 135 μl 15 . 13,000
 rpm 1 2
 DNA
 DNA 70%
 100 μl .

2) 중합효소연쇄반응

(polymorphism)

D₂

5' - CCGTCGACGGCTGGCCAAGTTGTCTA - 3'
 5' - CCGTCGACCCTTCTGAGTGTCATCA - 3'

RCR 25 μl 35

Template DNA	50ng
Primer	25pmole
MgCl ₂	1.5mM
Tris - Cl(pH 8.3)	10mM
KCl	50mM
Gelatin	0.1%(w/v)
dNTP	200 μ M
Taq polymerase	1U
Total	25 μl

94	10	1	94
1 , 50	1 , 72	1 30	35
	72	10 1	

3) 증폭된 생성물의 분석

A1 A2 PCR
 D₂ Taq I 5% PAGE
 ethidium bromide
 (ultraviolet transilluminator) , polaroid
 (polaroid, film 667)

3. 통계분석 방법

PCR
 D₂ DNA
 D₂
 Chi - square

, Chi - square

(conti -

nuity correction) Chi - square

결 과

1. 환자의 특성

(67) 27 70 46.
 49±9.28 , (100) 27
 67 45.33±8.74
 (Table 1).

가

2. 도파민 D₂ 수용체 유전자좌의 분석결과

D₂
 A1A1, A1A2, A2A2 3가
 67 A1A1 11 (16.4%), A1A2 30
 (44.8%), A2A2 26 (38.8%) 55.
 2% 44.8% 100
 A1A1 17 (17.0%), A1A2 42 (42.0%), A2A2 41
 (41.0%) 58.0% 42.
 0%
 A1 0.
 39 , 0.38
 D₂ A1
 ($\chi^2=0.128, p>.05$)(Table 2).

(Table 3, Fig. 1, 2).

Table 1. Demographic data

Group	N	Sex	Age (Mean ± SD)*
Alcoholics	67	Male	46.49 ± 9.28
Controls	100	Male	45.33 ± 8.74

* NS : Not-significant

Table 2. Distribution of genotypes and frequencies of Taq I polymorphism of the dopamine D₂ receptor gene in alcoholics and controls

Group	N	Taq I genotypes			Allele		Frequency of A1 allele
		A1A1 (%)	A1A2 (%)	A2A2 (%)	A1 (%)	A2 (%)	
Alcoholics	67	11 (16.4)	30 (44.8)	26 (38.8)	41 (61.2)	56 (83.6)	0.39
Controls	100	17 (17.0)	42 (42.0)	41 (41.0)	59 (59.0)	83 (83.0)	0.38

Chi-square=0.128 p=.938

고 찰

(1991) 가 D₂ 가 . Bolos (1990) Parsian PCR . Bolos (1990) D₂ A1

Table 3. Homogeneity and heterogeneity in dopamine D₂ receptor of alcoholics and controls

Group	N	Homogeneity	Heterogeneity
Alcoholics	67	37 (55.2%)	30 (44.8%)
Controls	100	58 (58.0%)	42 (42.0%)

Continuity Adjusted Chi-Square=0.038 p=0.845

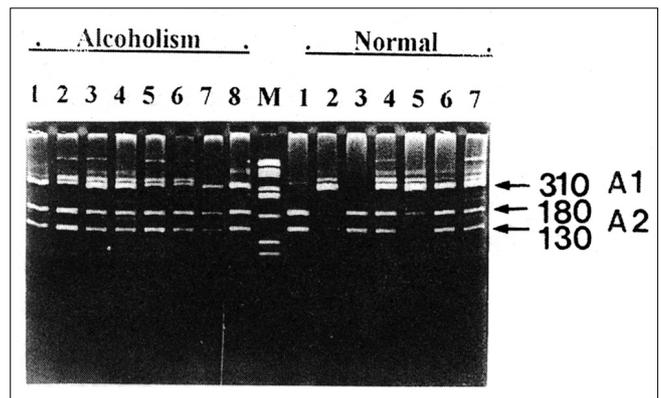


Fig. 1. PCR-Taq I PCR of Dopamine D₂ receptor alleles from Alcoholics and Controls. Patient No. 1 : A1A2 heterozygote, No. 2 : A1A2 heterozygote, No. 3 : A1A2 heterozygote, No. 4 : A1A2 heterozygote, No. 5 : A1A2 heterozygote, No. 6 : A1A2 heterozygote, No. 7 : A1A2 heterozygote, No. 8 : A1A2 heterozygote. M : pUC19 / Hae DNA size marker. Normal control No. 1 : A2A2 homozygote, No. 2 : A1A1 homozygote, No. 3 : A2A2 homozygote, No. 4 : A1A2 heterozygote, No. 5 : A1A1 homozygote, No. 6 : A1A2 heterozygote, No. 7 : A1A2 heterozygote. PCR products were run on a 5% PAGE / 0.5X TBE gel.

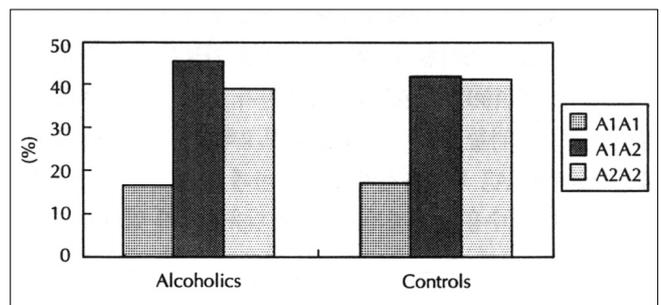


Fig. 2. Distribution of Dopamine D₂ receptor alleles.

가 . , 가 , 가 (No - D₂ ble Blum 1991). Gelernter (1991) Bolos (1990) 가 . Gelernter (1991) 가 , D₂ 가 가 (Blum 1991 ; Clon - 가 D₂ A1 가 ingner 1991 ; Parsian 1991). 가 . Cook (Blum 1991 ; Parsian 1991 ; (1992), Goldman (1992), Turner (1992) Turner 1992) D₂ , Gelernter (1991) . (Cloni - Blum (1990) 35 가 nger 1991 ; Noble Blum 1991 ; Smith 1991) D₂ A1 가 (69% 20%). Comings (1991) A1 (restriction fragment length poly - 가 가 , morphism ; RFLP) D₂ 가가 . A1 가 . Cloninger(1991) Noble(1993) Blum (1990) , 가 D₂ Bolos (1990), Noble Blum(1991) , 가, 가 A1 가가 . Parsian (1991) D₂ . **결 론** . 10 가 25 D₂ A1 (60% 12%). Blum (1990) . A1 (PCR) D₂ 가 . A1 가 . D₂ A1 Comings (1991) A1 가 . 중심 단어 : D₂ . D₂ A1 가 . A1 가 .

참고문헌

American Psychiatric Association (1987) : Diagnostic and Statistical

Manual of Mental Disorders, 3rd ed. Rev, Washington DC, American Psychiatric Association

- Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, Jagadeeswaran P, Nogami H, Briggs AH, Cohn JB(1990)** : Allelic association of human dopamine D₂ receptor gene in alcoholism. *JAMA* 263 : 2055-2060
- Blum K, Noble EP, Sheridan PJ(1991)** : Association of A1 allele of the D₂ dopamine receptor gene with severe alcoholism. *Alcoholism* 8 : 409-416
- Bolos AM, Dean M, Lucas-Derse S, Ramsburg M, Brown GL, Goldman D(1990)** : Population and pedigree studies reveal a lack of association between the dopamine D₂ receptor gene and alcoholism. *JAMA* 264 : 3156-3160
- Cloninger CR, Bohman M, Sigvardsson(1981)** : Inheritance of alcohol abuse. *Arch Gen Psychiatry* 38 : 861-868
- Cloninger CR(1991)** : D₂ dopamine receptor gene is associated but not linked with alcoholism. *JAMA* 266 : 1833-1834
- Comings DE, Comings BG, Muhleman D(1991)** : The dopamine D₂ receptor locus as a modifying gene in neuropsychiatric disorders. *JAMA* 266 : 1793-1800
- Cook BL, Wang ZW, Crowe RR, Hauser R, Freimer M(1992)** : Alcoholism and the D₂ receptor gene. *Alcohol Clin Exp Res* 4 : 806-809
- Gelernter J, O'Malley S, Risch N(1991)** : No association between an allele at the D₂ dopamine receptor gene (DRD2) and alcoholism. *JAMA* 266 : 1801-1807
- Goldman D, Dean M, Brown GL(1992)** : D₂ dopamine receptor genotype and cerebrospinal fluid homovanillic acid, 5-hydroxy-indoleacetic acid and 3-methoxy-4-hydroxyphenylglycol in Finland and the United States. *Acta Psychiatr Scand* 86 : 351-357
- Goodwin DS(1979)** : Alcoholism and heredity. *Arch Gen Psychiatry* 36 : 57-61
- Hill SY, Goodwin DW, Cadoret R, Osterland CK, Doner SM(1975)** : Association and linkage between alcoholism and eleven serological markers. *J Stud Alcohol* 36 : 981-992
- Hill SY, Aston C, Rabin B(1988)** : Suggestive evidence of genetic linkage between alcoholism and the NMS blood group. *Alcoholism* 12 : 811-814
- Koob GF, Bloom FE(1988)** : Cellular and molecular mechanisms of drug dependence. *Science* 242 : 715-723
- Lee T, Seeman P, Rajput A, Farley U, Hornykiewicz O(1978)** : Receptor basis for dopaminergic supersensitivity in Parkinson's disease. *Nature* 273 : 59-61
- Noble EP, Blum K(1991)** : The dopamine D₂ receptor gene and alcoholism. *Journal of the American Medical Association* 265 : 2667
- Noble EP(1993)** : The D₂ dopamine receptor gene : a review of association study in alcoholism. *Behavioral Genetics* 23 : 119-129
- Parsian A, Todd RD, Devor EJ(1991)** : Alcoholism and allele of the human D₂ dopamine receptor locus : studies of association and linkage. *Arch Gen Psychiatry* 48 : 655-663
- Schwab S, Soyka M, Niederecker M, Ackenheil M, Scherer J, Wildenauer DB(1991)** : Allelic association of human D₂-receptor DNA polymorphism ruled out in 45 alcoholics. *Am J Hum Genet* 49 (Suppl) : 203
- Seeman P, Ulpian C, Bergeron C, Riederer P, Jellinger K, Gabriel E, Reynolds GP, Tourtellotte WW(1984)** : Bimodal distribution of dopamine receptor densities in brains of schizophrenics. *Science* 225 : 728-730
- Sigeta Y, Ishii H, Takagi S, Yoshitake Y(1980)** : HLA antigens as immunogenetic markers of alcoholism and alcoholic liver disease. *Pharmacol Biochem Behav* 13 (Suppl 1) : 89-94
- Smith SS, Gorelick DA, O'Hara BF, Uhl GR(1991)** : The dopamine D₂ receptor gene and alcoholism. *JAMA* 265 : 2667-2668
- Turner E, Ewing J, Shilling P(1992)** : Lack of association between an RFLP near the D₂ dopamine receptor gene and severe alcoholism. *Biol Psychiatry* 31 : 285-290