

정신분열증, 알코올중독, 약물중독에서 도파민 D₂ 수용체 유전자의
조절유전자(modifying gene)로서의 역할
- 충동적 · 강박적 · 탐닉적 행동을 나타내는 정신질환들에서
도파민 D₂ 수용체의 조절유전자로서의 역할 -

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The Dopamine D₂ Receptor Locus as a Modifying Gene in Korean Schizophrenia,
Alcoholism and Drug Addiction

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ABSTRACT

The authors attempted to examine the allelic association between the A1 allele of Dopamine D₂ receptor and schizophrenia, alcoholism, drug addiction in Koreans. Schizophrenic patients(n=31), alcoholism(n=65), drug addiction(n=18) and controls(n=52) were examined by case-control study for distribution of the TaqI polymorphism of the dopamine D₂ receptor gene in Korean population to minimize the effect of racial differences in gene frequencies.

In schizophrenics, the numbers of schizophrenics with A1A1, A1A2, A2A2 were 9(29.0%), 15(48.4%) and 7(22.6%) respectively and in alcoholics with A1A1, A1A2, A2A2 were 14(21.5%), 36(55.4%) and 15(23.1%) respectively and in drug addiction with A1A1, A1A2, A2A2 were 2(11.1%), 10(55.6%) and 6(33.3%) respectively and in controls with A1A1, A1A2, A2A2 were 4(7.6%), 24(46.2%) and 24(46.2%) respectively. The prevalence of the A1 allele in schizophrenics, alcoholics, drug addiction and controls were 77%, 76.9%, 67% and 53.8% respectively. And the frequency of the A1 allele in schizophrenics, alcoholics, drug addiction and controls were 0.53, 0.49 0.39 and 0.31 respectively. There was significant difference in the frequency of the A1 allele between schizophrenics, alcoholics and controls.

We also classified our alcoholic population. For classification by severity, we used the median MAST score 30 in our samples. There was also significant difference in the frequency of the A1 allele between less severe group(0.42) and more severe group(0.57).

This data suggest that the A1 allele is associated with schizophrenia and alcoholism in Koreans. Furthermore the prevalence of the A1 allele increased in more severely affected alcoholics.

The authors conclude that our data support an allelic association between the A1 allele at dopamine D₂ receptor and schizophrenia, alcoholism. These results suggest the A1 allele of the DRD₂ gene is associated with a number of behavior disorders in which it may act as a modifying gene rather than as the primary etiological agent.

KEY WORDS : Schizophrenia · Alcoholism · Drug addiction · Dopamine D₂ receptor · Allelic association · Modifying gene.

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서론

가

D₂

(Cross 1981 ; Janowsky Davis 1976 ; Snyder 1973 ; Wong 1986), (Butler 1979 ; Cohen 1978 ; Feinberg Carrol 1979 ; Golden 1974 ; Jan-kovic 1984 ; Klawans 1978), (Goeders Smith 1983 ; Koob Bloom 1988 ; Snyder 1984) 가

D₂ A1 (A1 allele) 가 Blum (1990)

D₂ A1 (allele)가 A1 가 (A1 allele) (Arinami 1993 ; Blum 1990 ; Parsian 1991) (Bolos 1990 ; Gelernter 1991) A1 (prevalence) 가

D₂ A1 (allele)가

D₂ A1 (allele)가 (major gene) (modifying gene)

Comings (1991) D₂ A1 가

D₂ A1 가 (im-pulsive - compulsive - addictive behaviors) A1 가

A1 가 D₂ 가

가 (pol-

merase chain reaction ; PCR)(Saiki 1985)

study) D₂

(case - control Taq I

연구 대상 및 방법

1. 연구대상

1) 대상 환자군

1996 5 1997 5

57

20 DSM - (1994)

2

(1)

1996 5 1997 5

DSM - (APA 1994)

57

20

가 24 , 가 7

31 32.62

(2)

1996 5 1997 5

DSM -

35

(20 57)

(1990)

MAST(Michigan Alcoholism Screening Test) score

(less severe group)

(more severe group)

(median split)

median MAST score 30

(3)

1996 5 1997 5

DSM -

(substance dependence)

18

(20 57)

MAST score 7

(1985).
 2) 정상대조군
 52

Template DNA	50ng
Primers	25pmol
MgCl ₂	1.5mM
Tris - HCL(pH 8.3)	10mM
KCL	50mM
Ggelatin	0.1%(W/V)
DNTP	200 μ M
Taq polymerase	1U

가 MAST score 7
 52 가 36 , 가
 16 31.92 .

25 μl			
94	10	1	(cycle)
94	1	50	1, 72 1 30
35	(cycle)		72 10 1

2. 연구방법

1) Genomic DNA의 정제

2ml 13,000rpm 1
 (pellet) ACE shocking solution(NH₄
 Cl 8g, Na₂EDTAH₂O 1g, KH₂PO₄ 0.1g 1
) 500 μl 3
 2

3) 증폭된 생성물의 분석

A1 A2 PCR TaqI
 2% (agarous gel)
 ethidium bromide (ultravio-
 let transilluminator)

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

3. 통계분석방법

SASS Version 6.3
 2 × 2 2 × 3 Fisher
 exact test P - value
 p<0.05

2 DNA
 DNA 70%
 100 μl

	(prevalence)	(frequency)
Comings (1991)		
A1	A1A1	A1A2
		A1
A1	11	

2) 도파민 D₂ 수용체 유전자좌의 분석
 D₂ (polymorphism)
 (polymerase chain reaction ;
 PCR)(Saiki 1985) D₂
 (primer)

결 과

Forward
 5' - CCGTCGACGGCTGGCCAAGTTGTCTA - 3'
 Reverse
 5' - CCGTCGACCCTTCCTGAGTGTCA - 3'
 25 μl 35 (cycle)

Table 1

Table 1. Demographic data in schizophrenia, alcoholism and drug addiction

Diagnosis	N	Sex	Mean age ± SD (years)
Schizophrenia	31	24M, 7F	32.61 ± 6.69
Alcoholism	65	65M, 0F	41.28 ± 8.47
Drug addiction	18	18M, 0F	29.78 ± 7.53
Controls	52	36M, 16F	31.92 ± 5.77
Total	166	143M, 23F	35.70 ± 8.74

D₂ PCR TaqI

A1A1, A1A2, A2A2 37

52 A1A1 4 (7.69%), A1

A2 24 (46.15%), A2A2 24 (46.15%)

(homozygotics) 53.8% (heterozygotics) 46.15% (Fig. 1).

31 A1A1 9 (29.0%),

A1A2 15 (48.4%), A2A2 7 (22.6%)

51.6%, 48.4% (Fig. 2).

65 A1A1 15 (23.1%), A1A2 35 (53.85%), A2A2 15 (23.1%) 46.15%,

53.85% (Fig. 4).

18 A1A1 2 (6.5%), A1A2 10 (55.6%), A2A2 6 (33.3%) 44.4%, 55.6% (Fig. 3).

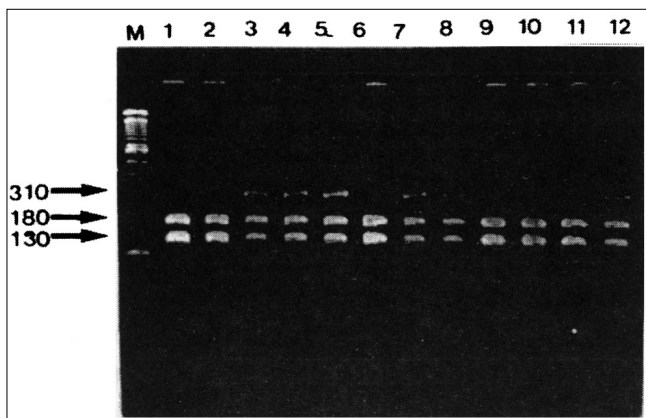


Fig. 1. PCR analysis of Taq I polymorphism in DRD2 allele from normal control.

No. 1 : homozygote A2/A2. No. 2 : homozygote A2/A2.
 No. 3 : heterozygote A1/A2. No. 4 : heterozygote A1/A2.
 No. 5 : heterozygote A1/A2. No. 6 : homozygote A2/A2.
 No. 7 : heterozygote A1/A2. No. 8 : heterozygote A1/A2.
 No. 9 : homozygote A2/A2. No. 10 : homozygote A2/A2.
 No. 11 : homozygote A2/A2. No. 12 : heterozygote A1/A2.
 M : 100bp DNA size marker.
 PCR products were run on a 5% PAGE/0.5 × TBE gel.

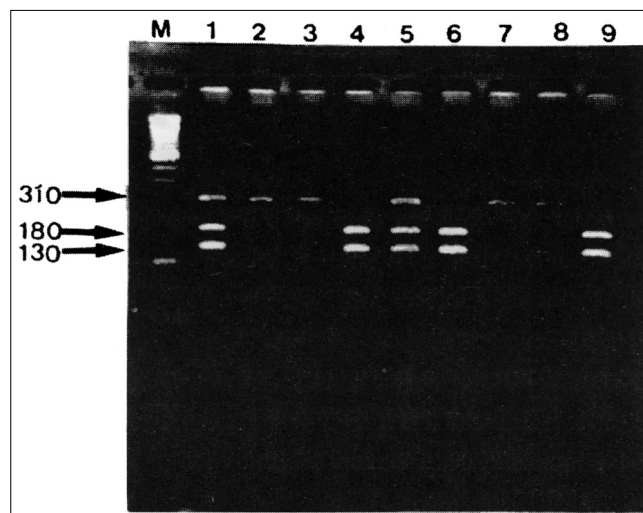


Fig. 3. PCR analysis of Taq I polymorphism in DRD2 allele from drug addiction.

No. 1 : heterozygote A1/A2. No. 2 : heterozygote A1/A2.
 No. 3 : homozygote A1/A1. No. 4 : homozygote A2/A2.
 No. 5 : heterozygote A1/A2. No. 6 : homozygote A2/A2.
 No. 7 : homozygote A1/A1. No. 8 : heterozygote A1/A2.
 No. 9 : homozygote A2/A2. M : 100bp DNA size marker.
 PCR products were run on a 5% PAGE/0.5 × TBE gel.

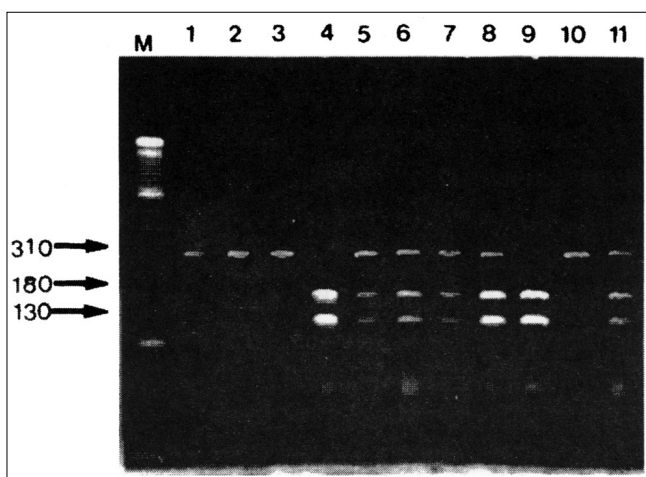


Fig. 2. PCR analysis of Taq I polymorphism in DRD2 allele from schizophrenia.

No. 1 : homozygote A1/A1. No. 2 : homozygote A1/A1.
 No. 3 : homozygote A1/A1. No. 4 : homozygote A2/A2.
 No. 5 : heterozygote A1/A2. No. 6 : heterozygote A2/A2.
 No. 7 : heterozygote A1/A2. No. 8 : heterozygote A1/A2.
 No. 9 : homozygote A2/A2. No. 10 : homozygote A1/A2.
 No. 11 : heterozygote A1/A2. M : 100bp DNA size marker.
 PCR products were run on a 5% PAGE/0.5 × TBE gel.

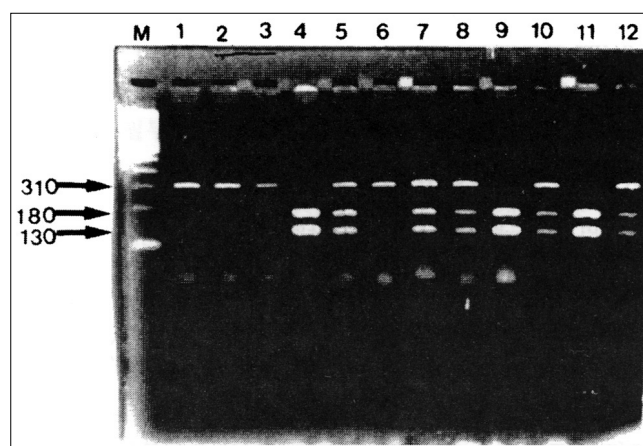


Fig. 4. PCR analysis of Taq I polymorphism in DRD2 allele from alcoholism.

No. 1 : heterozygote A1/A2. No. 2 : heterozygote A1/A2.
 No. 3 : homozygote A1/A1. No. 4 : homozygote A2/A2.
 No. 5 : heterozygote A1/A2. No. 6 : heterozygote A1/A2.
 No. 7 : heterozygote A1/A2. No. 8 : heterozygote A1/A2.
 No. 9 : homozygote A2/A2. No. 10 : heterozygote A1/A2.
 No. 11 : homozygote A2/A2. No. 12 : heterozygote A1/A2.
 M : 100bp DNA size marker.
 PCR products were run on a 5% PAGE/0.5 × TBE gel.

0.49 A1 76.9% A1 (1995)

53.8% 0.31 가 가 (0.29) (0.48) A1 가

(p=0.011, p=0.0096). D₂ A1 Blum (p=0.0038) 가

(1990) Bolos (1990) 가

가 Gelernter (1991), Schwab (1991), A1

Turner (1992) (DSM - -R) D₂ 가

Bolos (1990) (Di Bella)

(Noble 1991). 1994 ; Jonsson 1993), type I

Comings (1991) type

가 (22.2% 14.5%),

Amadeo (1993) 19.1% 28% (1995).

가

21.73% 22.39%, 21.98% , 가 가

45.56%, 2.23% 가

(1994).

MAST 가 (Stephen 1975 ;

Tsuang 1980), (Shenton 1989 ; Tsu -

Bolos (1990) ang 1991)

median MAST score , 가

median MAST score 30 (less

severe group) (more severe group) (Kinney 1986), (Fran -

61.3%, 91.2% 0.42, 0.57 ke 1992), 가 D₂ A1

가 (p=0.006, 0.012). A1 가

가

가 MAST

Parsian (1991) 가 A1

(0.31 0.39) 가

(12% 60%) Arinami (1993) Par - 가

sian (1991) , 가

A1 가 D₂ 가

(77% 59%). (Blum A1 가

1991 ; Parsian 1991 ; Turner 1992) (Geler -

nter 1991) A1 가 0.31

가 0.29(1995) Blum

(1990) A1 가 Caucasian Black

Barr Kidd(1993) A1

A1 0.53 가 0.09 0.75

0.31 가 A1

(p=0.015). Comings (1991) 0.31 Caucasian 0.21(Grandy 1989),

0.20(Bolos 1990), 0.06(Parsian 1991) As- median MAST sco-
 0.42(Arinami 1993) re
 Blum (1990) 가 Comings (1991) A1
 Schwab (1991) 가 (modifying gene)
 가 가

결론

D₂ A1 가 D₂
 가 (autosomal chrom- D₂ A1
 some) 가 (less severe group)
 (Parsian 1991). MAST (more severe group)
 가 가
 중심 단어 : D₂
 가 가 10 가

참고문헌

(heterog- (Cloninger 1991)
 eneity) (multigeneity) 가
 가 D₂
 A1 가 가 (susceptibility) 가
 가 A1 가 가
 A1 가 가 가
 가 가 A1 가 , A1
 가 D₂ A1 가

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