

한국인 알코올 중독환자에서 도파민 D4 수용체의 대립 유전자 연관성에 대한 연구

유 승 호* · 이 민 수**†

Allelic Association of the Dopamine D4 Receptor Gene in Korean Alcoholism

Seung Ho Ryu, M.D.,* Min Soo Lee, M.D.**†

ABSTRACT

The dopamine D4 receptor gene has a hypervariable segment in the coding region characterized by a varying number of 48bp repeats in exon 3 of the gene. Varying the numbers of repeated segments may change the length, structure, and function of the receptor, which makes this gene a possible candidate for variations in dopamine-related behaviors, such as alcoholism and drug abuse.

We evaluated the dopamine D4 receptor genotype in male alcoholics and normal controls. All alcoholics and controls were unrelated and from the Korean population. Genotype and allele frequencies in 67 alcoholics were compared to 67 controls who were free of alcohol abuse, substance abuse, and major mental illness. No association was found between the dopamine D4 receptor allele and alcoholism.

This result indicates that there is no association of the dopamine D4 receptor with alcoholism in Korean. Further systemized investigation to determine the role of dopamine D4 receptor gene in alcoholism with a larger sample size will be required.

KEY WORDS : Alcoholism · Dopamine D4 receptor · Genotype · Allele.

서 론

1981 ; Goodwin 1979 ; Merikangas 1990).

가

, 가
(Cloninger

(nucleus accumbens)

Department of Psychiatry, Konkuk University College of Medicine,
Seoul, Korea

(Koob Bloom 1988 ; Moolten Kornetsky
1990 ; Strange 1993 ; Wise Rompre 1989).

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

†교신저자 : , 136 - 705 5가 126 - 1
) (02) 920 - 5354,) (02) 923 - 3507
E - mail) leeminso@korea.ac.kr

ador - Woodruff 1994),

D2

A1 (allele) 67
 (Arinami 1993 ; Blum 1990).
 D4 G - mRNA
 가 (olfactory tubercle)
 (De Keyser 1993 ; Van Tol 1991). 67
 D4 D2 D3
 D4
 clozapine octoclothePIN D2
 D3 10 가 (Van Tol
 1991). D4 D2
 D4 가 Gi Go -
 , adenyI cyclase (De
 Keyser 1993 ; Strange 1993). D4
 D4
 (polymorphism)
 exon 48bp (rep-
 eats)(2 8 10) (Lichter
 1993). D4
 , D4
 (Van
 Tol 1992).
 , D4
 D4
 48bp
 가 , ALDH2
 (aldehyde dehydrogenase 2 gene)
 가
 (Adamson
 1995 ; Bau 2001 ; Chang 1997 ; George 1993 ;
 Hill 1999 ; Muramatsu 1996 ; Sander 1997 ; Sulli-
 van 1998).
 67
 D4 48bp

연구대상 및 방법

1. 연구대상

DSM - (APA 1994)

2. 연구방법

1) Genomic DNA의 정제

1.5ml 13,000rpm 1
 pellet ACE shocking solution(NH₄Cl 8g,
 Na₂EDTAH₂O 1g, KH₂PO₄ 0.1g 1l)
 500 μl 3
 2
 pellet 400 μl nucleic
 lysis Buffer[Tris(pH8.0) 10mM, NaCl 400mM, EDTA 2
 mM] pellet 10% SDS 27 μl
 proteinase K 10 μl 가 56 2
 saturated NaCl 135 μl 15
 13000rpm 1
 2 DNA
 DNA 70%
 D4 100 μl

2) 중합효소연쇄반응을 이용한 유전자형의 판별

D4
 (Polymerase Chain Reaction : PCR)
 D4
 D4 - 3 : 5 ' - GCG ACT ACG TGG TCT ACT CG - 3 '
 D4 - 42 : 5 ' - AGG ACC CTC ATG GCC TTG - 3 '
 PCR 50 μl 35

Takara GC buffer	25 μl
Takara LA Taq	1.5U
each Primer	each 20pmol/50 μl
dNTP(2.5mM each)	8 μl
Template DNA	200ng
Total	50 μl

94 5 1 94
 30 , 58 30 , 72 30 35

Table 1. Demographic data

Group	N	Sex	Age (Mean ± SD)*
Alcoholics	67	Male	46.49 ± 9.28
Controls	67	Male	46.40 ± 9.14

*NS : Not-significant

72 5 1

3) 증폭된 생성물의 분석

D4 48bp
5% poly acrylamide ethidium
bromide (ultraviolet transill-
uminator) polaroid (polaroid, film 667)

4) 증폭된 생성물(PCR product)의 크기

Size of product : 474bp 522bp 570bp 618bp 666bp
714bp

3. 통계분석

D4
Chi - square

결 과

1. 환자의 특성

27~70 46.49(±9.28)
28) , 27~67 (1).
46.40(±9.14) 가

2. 도파민 D4 수용체 유전자좌의 분석결과

(67) D4
4 - repeat 가 96 (71.6%) 가 가 D4
, 4 - repeat 가 101 (75.4%) 가 , D2
가 . 2 - repeat 가 (Blum 1990 ; Cloninger 1991 ;
31 (23.1%) 27 (20.1%) Comings 1991 ; Noble 1992 ; Parsian 1991). Bl-
. 5 - repeat 6 (4.5%) um (1990) 35 가
5 (3.7%) . 3 - repeat D2 A1 가
1 (0.7%) . (2).
D4 2/2, 2/4, 2/5, 3/4, 4/4, (Bolos 1991 ; Gelernter 1993 ; Goldman 1991 ;
4/5 Turner 1992). , D2

Table 2. Dopamine D4 receptor allele frequencies for different numbers of 48 basepair repeat units*

Allele	Alcoholics	Controls	Total
2-repeat	31 (23.1)	27 (20.1)	58 (21.6)
3-repeat	1 (0.7)	1 (0.7)	2 (0.7)
4-repeat	96 (71.6)	101 (75.4)	197 (73.5)
5-repeat	6 (4.5)	5 (3.7)	11 (4.1)
Total	134 (100)	134 (100)	268 (100)

* : Data are numbers(%) of alleles

Table 3. Dopamine D4 receptor genotype frequencies for different numbers of 48 basepair repeat units*

DRD4 genotype	Alcoholics	Controls	Total
2/2	2 (3.0)	2 (3.0)	4 (3.0)
2/4	25 (37.3)	22 (32.8)	47 (35.1)
2/5	2 (3.0)	1 (1.5)	3 (2.2)
3/4	1 (1.5)	1 (1.5)	2 (1.5)
4/4	33 (49.3)	37 (55.2)	70 (52.2)
4/5	4 (6.0)	4 (6.0)	8 (6.0)
Total	67 (100)	67 (100)	134 (100)

* : Data are numbers(%) of genotypes

(3).

고 찰

가 (Devor Cloninger 1989 ; Gelernter 1993 ; Goodwin 1991 ; Gordis 1990).
(Gordis 1990 ; Holden 1991).

가 Muramatsu (1996)

D3
(protective factor) ALDH2

A1 가 가 가 80 48bp D4 5 -
D3 repeat 가
(Gorwood 1995 ; Parsian 1997 ; Sander 1995). Kotler (1997)

(novelty seeking)

D4 (7 - repeat)

4 - repeat 2 - repeat

가

4 - repeat 2 - repeat 가 D4
(Chang 1997 ; Muramatsu 1996). 2001 ; Sander 1997 ; Sullivan 1998). (Bau 1999 ; Bau

Adamson (1995) 4 - repeat D4

Sander (1997) , ALDH2

4 - repeat 7 - repeat 가

D4 48bp D4

D2 가
(Barr Kidd 1993).

D4 , ,

D4 가

(Parsian 1997),
(Adamson 1995) 3 중심 단어 : D4

(Chang 1997)
George (1993)

D4 repeat - 3 repeat - 6 가

가

D4 George (1993)

repeat - 6 가 4 repeat -

6 가 1 Ad-

amson (1995) 1 ,

George (1993) D4

D4

참고문헌

- Adamson MD, Kennedy J, Petronis A, Dean M, Virkkunen M, Linnola M, Goldman D(1995) : *DRD4 dopamine receptor genotype and CSF monoamine metabolites in Finnish alcoholics and controls. Am J Med Genet 60 : 199-205*
- Arinami T, Itokawa M, Komiyama T, Mitsushino H, Mori H, Mifune H, Hamaguchi H, Toru M(1993) : *Association between severity of alcoholism and the A1 allele of the dopamine D2 receptor gene TaqI A RFLP in Japanese. Biol Psychiatry 33 : 108-114*
- Barr CL, Kidd KK(1993) : *Population frequencies of the A1 allele at the dopamine D2 receptor locus. Biol Psychiatry 34 : 204-209*
- Bau CH, Roman T, Almeida S, Hutz MH(1999) : *Dopamine D4 receptor gene and personality dimensions in Brazilian male alcoholics. Psychiatr Genet 9 : 139-143*
- Bau CH, Almeida S, Costa FT, Garcia CE, Elias EP, Ponso AC, Spode A, Hutz MH(2001) : *DRD4 and DAT1 as modifying genes in alcoholism : Interaction with novelty seeking on level of alcohol consumption. Mol Psychiatry 6 : 7-9*
- Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, Jagadees-

- waran P, Nogami H, Briggs AH, Cohn JB(1990) : Allelic association of human dopamine D2 receptor gene in alcoholism. *JAMA* 263 : 2055-2060
- Bolos AM, Dean M, Lucas-Deprse S, Ramsburg M, Brown GL, Goldman D(1991) : Population and pedigree studies reveal a lack of association between the dopamine D2 receptor gene and alcoholism. *JAMA* 264 : 3156-3160
- Chang FM, Ko HC, Lu RB, Pakstis AJ, Kidd KK(1997) : The dopamine D4 receptor gene(DRD4) is not associated with alcoholism in three Taiwanese populations : six polymorphisms tested separately and as haplotypes. *Biol Psychiatry* 41 : 394-405
- Cloninger CR(1991) : D2 dopamine receptor gene is associated but not linked to alcoholism. *JAMA* 256 : 1833-1834
- Cloninger CR, Bohman M, Sigvardsson S(1981) : Inheritance of alcohol abuse. *Arch Gen Psychiatry* 38 : 861-868
- Comings DE, Comings BG, Muhleman D, Dietz G, Shahbagrami B, Tost D(1991) : The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. *JAMA* 266 : 1793-1800
- De Keyser J(1993) : Subtypes and localization of dopamine receptors in the human brain. *Neurochem Int* 22 : 82-92
- Devor EJ, Cloninger DR(1989) : Genetics of alcoholism. *Annu Rev Genet* 23 : 19-36
- Gelernter J, Goldman D, Risch N(1993) : The A1 allele at the D2 dopamine receptor gene and alcoholism. *JAMA* 269 : 1673-1677
- George SR, Cheng R, Nguyen T, Israel Y, O'Dowd GF(1993) : Polymorphisms of the D4 dopamine receptor alleles in chronic alcoholism. *Biochem Biophys Res Commun* 196 : 107-114
- Goldman D, Brown GL, Bolos AM, Lucas-Deprse S, Dean M(1991) : The dopamine D2 receptor gene and alcoholism. *JAMA* 265 : 2668
- Goodwin D(1979) : Alcoholism and Heredity. *Arch Gen Psychiatry* 36 : 57-61
- Goodwin D(1991) : The genetics of alcoholism. In *Genes, Brain, and Behavior*, Ed by McHugh PR and McKusick VA, New York, Raven Press Ltd, pp219-226
- Gordis E, Tabakoff B, Goldman D, Berg K(1990) : Finding the gene(s) for alcoholism. *JAMA* 263 : 2094-2095
- Gorwood P, Matres MP, Ades J, Sokoloff P, Noble EP, Geijer T, Blum K, Neiman J, Jonsson E, Feingold J, Schwartz JC(1995) : Lack of association between alcohol dependence and D3 dopamine receptor gene in three independent samples. *Am J Med Genet* 60 : 529-531
- Hill SY, Zezza N, Wipprecht G, Xu J, Neiswanger K(1999) : Linkage studies of D2 and D4 receptor genes and alcoholism. *Am J Med Genet* 88 : 676-685
- Holden C(1991) : Probing the complex genetics of alcoholism. *Science* 251 : 163-164
- Koob GF, Bloom FE(1988) : Cellular and molecular mechanisms of drug dependence. *Sci* 242 : 715-723
- Kotler M, Cohen H, Segman R, Gritsenko I, Nemanov L, Lerer B, Kramer I, Zer-Zion M, Kletz I, Ebstein RP(1997) : Excess dopamine D4 receptor(D4DR) exon III seven repeat allele in opioid-dependent subjects. *Mol Psychiatry* 2 : 251-254
- Lichter JB, Barr CL, Kennedy JL, Ban Tol HH, Kidd KK, Livak KJ(1993) : A hypervariable segment in the human dopamine receptor D4(DRD4) gene. *Hum Mol Genet* 2 : 767-773
- Meador-Woodruff JH(1994) : Update on dopamine receptors. *Ann Clin Psychiatry* 6 : 79-90
- Merikangas KR(1990) : The genetic epidemiology of alcoholism. *Psychol Med* 20 : 11-22
- Moolten M, Kornetsky C(1990) : Oral self-administration of ethanol and not experimenter-administrated ethanol facilitates rewarding electrical brain stimulation. *Alcohol* 7 : 221-225
- Muramatsu T, Higuchi S, Mrayama M, Matsushita S, Hayashida M(1996) : Association between alcoholism and the dopamine D4 receptor gene. *J Med Genet* 33 : 113-115
- Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ(1992) : Allelic association of the D2 dopamine receptor gene with receptor binding characteristics in alcoholism. *Arch Gen Psychiatry* 48 : 648-654
- Parsian A, Todd RD, Devor EJ, O'Malley KL, Suarez BK, Cloninger CR(1991) : Alcoholism and allele of the human D2 dopamine receptor locus. *Arch Gen Psychiatry* 48 : 655-663
- Parsian A, Chakraverty S, Fisher L, Cloninger CR(1997) : No association between polymorphisms in the human dopamine D3 and D4 receptor genes and alcoholism. *Am J Med Genet* 74 : 281-285
- Sander T, Harms H, Podschus J, Finekh U, Nickel B, Rolfs A, Rommelspacher H, Schmidt LG(1995) : Dopamine D1, D2, and D3 receptor genes in alcohol dependence. *Psychiatr Genet* 5 : 171-176
- Sander T, Harms H, Dufeu P, Kuhn S, Rommelspacher H, Schmidt LG(1997) : Dopamine D4 receptor exon III alleles and variation of novelty seeking in alcoholics. *Am J Med Genet* 74 : 483-487
- Strange P(1993) : New insights into dopamine receptors in the CNS. *Neurochem Int* 22 : 223-231
- Sullivan PF, Fifeild WJ, Kennedy MA, Mulder RT, Sellman JD, Joyce PR(1998) : No association between novelty seeking and the type 4 dopamine receptor gene(DRD4) in two New Zealand samples. *Am J Psychiat* 155 : 98-101
- Turner E, Eving J, Shilling P, Smith TL, Irwin M, Schuckit M, Kelose JR(1992) : Lack of association between an RFLP near the D2 dopamine receptor gene and severe alcoholism. *Biol Psychiatry* 31 : 285-290
- Van Tol HH, Bunzow JR, Gue H, Sunahara RK, Seeman P, Niznik H, Civelli O(1991) : Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. *Nature* 350 : 610-614
- Van Tol HH, Wu CM, Guan HC, Ohara K, Bunzow JR, Civelli O, Kennedy J, Seeman P, Niznik HB, Jovanovich V(1992) : Multiple dopamine D4 receptor variants in the human population. *Nature* 358 : 149-152
- Wise RA, Rompre PP(1989) : Brain dopamine and reward. *Annu Rev Psychol* 40 : 191-225