

정신분열병 환자의 도파민 D₅ 수용체 유전자형과 치료반응과의 연관강성민* · 이민수*[†] · 이충순**The Association between the Dopamine D₅ Receptor Genotype and Treatment Response for Korean Schizophrenic PatientsSung Min Kang, M.D.,* Min Soo Lee M.D., Ph.D.,*[†] Choong Soon Rhee, M.D., Ph.D.**

ABSTRACT

Background : Dopamine receptors are strong candidates for involvement in schizophrenia and are target of a wide variety of antipsychotics. Dopamine D₅ receptor(DRD5) gene polymorphisms may be associated with various treatment response. The purpose of our study was define to what significance can be held as a predictor of treatment response in this polymorphism.

Method : The total number of 116 Korean chronic schizophrenic patients was assessed after 48 weeks treatment. The Positive and Negative Syndrome Scale(PANSS) was rated for the clinical response to various antipsychotics. With the use of polymerase chain reaction amplification, we assessed this dopamine D₅ receptor polymorphism in schizophrenic patients who had been treated with antipsychotics, and related genotype with treatment response, to test the hypothesis that DRD5 polymorphism may lead to varying response to antipsychotics.

Result : DRD5 polymorphism was not associated with treatment response to a variety of antipsychotics in chronic schizophrenic patients.

Conclusion : Genetic variation of D₅ receptors do not predict treatment response to antipsychotics.

KEY WORDS : Dopamine D₅ receptor · Receptor gene · Schizophrenia · Treatment response.

서 론 (Tsuang 1982). 가

가 가 . 가

가 (Krapelin 1907) 가 . 가 (linkage)

(association) 가 (Coom 1993 ; Ra-vindranathan 1994 ; Saha 1994).

D₂ (allele) clozapine

D₄

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

Yong-In Mental Hospital, Kyunggi-do, Korea

[†] : , 136 - 705 5가 126 - 1) (02) 920 - 5354,) (02) 923 - 3507

(Mana 1998 ; Peter 1994)
 clozapine
 (Arranz 1998)가
 clozapine
 가 .
 가
 가 가
 가
 (Crow 1987 ; Seeman 1987)
 가
 D₅
 가
 D₅
 (1999)
 DRD5 T978C
 T978C 가 가
 T978C 가
 D₅
 (Sommer
 1993). D₅ 가
 (Seeman 1993),
 D₅ 가
 가
 D₅

연구대상 및 방법

1. 연구대상

1998 4 1999 3
 18 65
 4 (DSM -)
 116

2. 연구방법

1) 유전자형 분석

(1) Genomic DNA

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(pH 8.0) 10mM, NaCl 400mM, EDTA
 2mM] pellet 10% SDS 27 μl
 proteinase K 10 μl 가 56 2
 saturated NaCl 135 μl 15
 13000rpm 1
 2 DNA
 DNA 70%
 100 μl

(2) (Polymerase Chain Reaction : PCR)

DRD5 (mutation)
 T978C Sommer (1993)
 (Polymerase Chain Reaction :
 PCR) T978C
 (primer) Sommer (1993)
 2 가
 (upstream) 가

I(5' - CCGGAGGGCCTTCG - 3') III(5' - CCTG -
 GGAGGAGGACT - 3') C
 II(5' - CCGGAGGGCCTTCA - 3') III(5' - CC -
 TGGGAGGAGGACT - 3') T

PCR (10mM Tris HCl(pH 8.3).
 50mM KCL. 1.5mM MgCl₂ 0.01% gelatin)2.5ul 200 uM
 dNTP. primer 0.1uM. DMSO 10%(w/v). Taq polyme -
 rase 0.5 units. template DNA 250 500ng
 25ul 94
 30 , 50 30 , 72 30 30

72 10 1

2) 임상증상의 평가

가 48 Positive and Negative Syndrome Scale (PANSS) Kay (1987)

PANSS 가
48 20%
가 가 가
가 workshop video
tape 가 가 0.8

3. 통계분석

a1a1, a2a2) chi-square
SPSS/PC+ version 10.0
0.05

결 과

1. 인구사회학적 특성

116 (69 , 47)
30 (18 , 12)

Table 1. Demographic data in samples of Korean schizophrenic patients

| | Responders N = 30(25.9%) | Non-responders N = 86(74.1%) |
|---|-----------------------------|---------------------------------|
| Sex | | |
| Male | 18(26.1%) | 51(73.9%) |
| Female | 12(25.5%) | 35(74.5%) |
| Age (yrs) | 39.03 ± 5.69 | 39.60 ± 7.65 |
| Age of onset (yrs) | 22.53 ± 5.50 | 22.60 ± 6.20 |
| Type | | |
| Paranoid | 13(29.5%) | 31(70.5%) |
| Disorganized | 3(15.0%) | 17(85.5%) |
| Catatonic | 1(100%) | 0(0) |
| Undifferentiated | 10(25.0%) | 30(75.0%) |
| Residual | 3(27.3%) | 8(72.7%) |
| Family history | | |
| Present | 2(18.2%) | 9(81.8%) |
| Unknown | 15(29.4%) | 36(70.6%) |
| None | 13(24.1%) | 41(75.9%) |
| Previous hospitalization | 2.88 ± 1.61 | 4.16 ± 2.82 |
| Dosage (Chlorpromazine used as control) | 1146 ± 678mg | 1165 ± 779mg |

() : %

86 (51 , 35)

39.03 ± 5.69 , 39.60 ± 7.65
22.53 ± 5.50 , 22.60 ± 6.20
, 가

(가
) 1146 ± 678mg, 1165 ± 779mg
(1).

2. DRD5의 유전자형에 따른 분포

a1a1 25 21.6%, a1a2 67 57.7%,
a2a2 24 20.7% a1 a2
79.3%, 78.4% (2).

3. DRD5 유전자형과 치료반응과의 관계

48 PANSS
. a1a1
PANSS
(: 13.3%,
: 24.4%) 가
. a1a2 63.3%,
55.9% 가
. a2a2 가
(: 23.3%, 19.8%).

Table 2. Dopamine D5 receptor genotype in samples of Korean schizophrenic patients

| Genotype | | | Total |
|----------|-------|-------|-------|
| a1a1 | a1a2 | a2a2 | |
| 25 | 67 | 24 | 116 |
| 21.6% | 57.7% | 20.7% | 100% |

Table 3. Dopamine D5 receptor genotype and treatment response in samples of Korean schizophrenic patients

| Genotype | Responder | Non-responder |
|---------------------|--------------|---------------|
| a1a1 | 4(13.3%) | 21(24.4%) |
| a1a2 | 19(63.3%) | 48(55.9%) |
| a2a2 | 7(23.3%) | 17(19.8%) |
| Total | 30(100.0%) | 86(100%) |
| Chi-square(p-value) | 1.623(0.444) | |
| Allele | | |
| A1 | 27(45.0%) | 90(52.3%) |
| A2 | 33(55.0%) | 82(47.7%) |
| Total | 60(100.0%) | 172(100.0%) |
| Chi-square(p-value) | 0.955(0.328) | |

() : %

(3).

고 찰

가 가

가

D₅

가

가

가

(Posi -

D₅

48

tron Emission Tomography ; PET)

가 PANSS

D₂

가 가

가

a1a1

(Seeman 1987).

a1a2, a2a2

가

가

D₅

(Shaikh 1994 ;

Rietschel 1996).

(Mana 1998).

D₅

D₁

D₁

가

D₂

(Rao 1991).

(Okubo 1997) D₁ 가

Wisconsin card sorting test

D₁

SCH

가

가

39166

가 (Den Boer 1995).

가

D₅

1 (functional gene) 2 가

(pseudo gene)가 , 4p 16.1, 2p 11.1 - p

11.2, 1q 21.1 (Grandy

1992 ; Nguyen 1991).

D₅

m - RNA D₁ , D₄

(stria -

tum) 가 (Rappaport 1993).

D₅

가

D₅

D₁

10

D₁

D₄

가

(Weinshank 1991)

D₂

D₅

가

D₅

가

(Arranz 1998).

가

(Sobell 1995 ; Sommer 1993),

116

(1999) -

D₅

D₅

중심 단어 : D₅

참고문헌

- 김준모 · 조주연 · 박두병 (1999) : 정신분열병에서의 도파민 D₅ 수용체 유전자 염기배열 변이(T978C)에 관한 연관연구. *신경정신의학* 38 : 399-407
- American Psychiatric Association(1994)** : *Diagnostic and Manual of Mental disorders, 4ed.* American Psychiatric Association, Washington
- Arranz MJ, Munro J, Owen MJ, Spurlock G, Sham P(1998)** : Evidence for association between polymorphism in the promoter and coding regions of the 5-HT_{2A} receptor gene and response to clzapine. *Mol Psychiatry* 3 : 61-66
- Coom H, Byerley W, Hoilk J, Hoff M, Myles-Worsley M, Lannfelt L, Sokoloff P, Schwartz JC, Waldo M, Freedman R, Plaetke R(1993)** : Linkage analysis of schizophrenia with five dopamine receptor genes in nine pedigree. *Am J Hum Genet* 52 : 327-334
- Crow TJ(1987)** : The dopamine hypothesis survives, but there must be a way ahead. *Br J Psychiatry* 151 : 460-465
- Den Boer JA, van Megen HJ, Fleischhacker WW, Louwerens JW, Slaap BR, Westenberg HG, Burrows GD, Srivastava ON (1995)** : Differential effects of the D₁-DA receptor antagonist SCH39166 on positive and negative symptoms of schizophrenia. *Psychopharmacology(Berl)* 121 : 317-322
- Grandy DK, Allen LJ, Zhang Y, Magenis RE and Civelli O(1992)** : Chromosomal localization of three human D₅ dopamine receptor genes. *Genomics* 13 : 968-973
- Kay SR, Fiszbein A, Opler LA(1987)** : The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 13 : 261
- Mana J, Arranz, Tao Li, J, Munro, X, Robin Murray, David A, Collier(1998)** : Lack of association between a polymorphism in the promoter region of the dopamine-2 receptor gene and clozapine response. *Pharmacogenetics* 8 : 481-484
- Nguyen TV, Jonathan B, Hui J, Domenica T, David CW, James LK, Richard W, Philips S, Brian FO(1991)** : Human dipamine D₅ receptor pseudogenes. *Gene* 109 : 211-218
- Okubo Y, Suhara T, Suzuki K(1997)** : Decreased prefrontal dopamine D₁ receptors in schizophrenia revealed by PET. *Nature* 385 : 634-636
- Peter A. Rao, David Picker, Pabli V Gejmen, Anca Ram, Eliot S. Gershon, Joel Gelernter(1994)** : Allelic variation in the D₄ Dopamine receptor(DRD4) gene does not predict response to clozapine. *Arch gen psychiatry* 51 : 912-917
- Rao PA, Molinoff P, Joyce JN(1991)** : Ontogeny of dopamine D₁ and D₂ receptor subtype in rat basal ganglia : a quantattive autographic study. *Dev Brain Res* 60 : 161-177
- Rappaport MS, Sealfon SC, Prikhozhan A, Huntly GW, Morrison JH(1993)** : Heterogenous distribution of D₁, D₂ and D₅ receptor mRNAs in monkey striatum. *Brain Res* 616 : 242-250
- Ravindranathan A, Coom H, Delisi L, Holik A, Hoff M, Brown A, Shields G, Crow T(1994)** : Linkage analysis between schizophrenia and a microsatellite polymorphism for the dopamine D₅ receptor gene. *Psychiatr Genet* 4 : 77-80
- Rietschel M, Naber D, Oberlander H, Jolzbach R, Finners R, Eggermann K(1996)** : Efficacy and side effects of clozapine : Testing for association with allelic variation in the dopamine D₄ receptor gene. *Neuropsychopharmacology* 15 : 491-496
- Saha N, Tsoi WF, Low PS, Basair J, Tay JSH(1994)** : Lack of association of dopamine D₃ receptor gene polymorphism in Chinese schizophrenic males. *Psychiatr Genet* 4 : 201-204
- Seeman P(1987)** : Dopamine receptors and the dopamine hypothesis of schizophrenia. *Synapse* 1 : 133-152
- Seeman P(1993)** : Schizophrenia as a brain disease. *Arch Neurol* 50 : 1093-1095
- Shaikh S, Gill M, Owen M, Asherson P, McGuffin P, Nanko S (1994)** : Failure to find linkage between a functional polyorphism in the dopamine D₄ receptor gene and schizophrenia. *Am J Med Genet* 54 : 8-11
- Sobell JL, Lind TJ, Sigurdson DC, Zald DH, Snitz BE, Growe WM, Heston LL, Sommer SS(1995)** : Dopamine D₅ receptor gene in schizophrenia : Identification of a nonsense change and multiple messense changes but lack of association with disease. *Hum Mol Genet* 4 : 507-514
- Sommer SS, Sombell JL, Heston LL(1993)** : A common exonic polymorphism in the human D₅ dopamine receptor gene. *Hum Genet* 92 : 633-634
- Tsuang MT, Bucher KD, Fleming JA(1982)** : Testing the monogenic theory of schizophrenia : an application of segregation analysis to bind family study data. *Br J Psychiatry* 140 : 595-599
- Weinshank RL, Adham N, Macchi M, Olsen MA, Brancheck TA, Harti PR(1991)** : Molecular cloning and characterization of a high affinity dopamine receptor and its pseudogene. *J Biol Chem* 266 : 22427-22435
- World Health Organization(1992)** : *The ICD-10 Classification of Mental and Behavioral Disorders : Clinical Descriptions and Diagnostic Guidelines.* World Health Organization, Geneva