

정신분열병환자에서 *Taq I A* 도파민 D_2 수용체 다형성과 항정신병약물의 치료반응과의 연관*

강 철 중**†

The Relationship between *Taq I A* Dopamine D_2 Receptor Polymorphism and Therapeutic Response to Antipsychotics in Schizophrenic Patients*

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ABSTRACT

Purpose : In an attempt to predict the interpersonal differences of therapeutic response to antipsychotic drugs on pharmaco - genetic bases, this study was designed to investigate the relationship between the therapeutic response to antipsychotic drugs and *Taq I A* dopamine D_2 receptor polymorphism in schizophrenic patients.

Methods : The subjects were 158 patients diagnosed with schizophrenia(DSM - IV). The therapeutic response to antipsychotic drugs was evaluated using the Treatment Response Scale(TRS) retrospectively. Patients were divided into two groups, dopamine receptor antagonist responders, and serotonin - dopamine antagonist responders. The patients' *Taq I A* dopamine D_2 receptor polymorphism was determined by polymerase chain reaction(PCR) and restriction fragment length polymorphism(RFLP).

Results : The dopamine receptor antagonist responders had the A1 allele in significantly higher incidences ($\chi^2(1)=4.875, p=0.027$, two - tailed). No significant difference was found among the serotonin - dopamine antagonist responders between those with or without the A1 allele.

Conclusions : The patients with the A1 allele responded better to dopamine receptor antagonists than those with no A1 allele. Based on these results, it is suggested that the pharmacological effect of dopamine receptor antagonists can be predicted depending on the presence of the A1 allele in schizophrenic patients.

KEY WORDS : Schizophrenia · Dopamine D_2 receptor polymorphism · *Taq I A* allele.

* 16th Congress of the European College of Neuropsychopharmacology, Prague, Czech Republic, September 20 - 24, 2003

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서 론

가

2004

1)

Chlorpromazine, Haloperidol 1

” 2

가

가

D₂ Taq I A

in vivo in vitro D₂ 8)

D₂ Taq I A Schæer 9)

haloperidol Taq I A

A , A2/A2

가 (A1/A2) 가

가

, Suzuki nemonap-

ride¹⁰⁾ bromperidol¹¹⁾

D₂ Taq I A

가 D₂

가

D₂ Taq I A

연구대상 및 방법

1. 연구대상

2001 12 2002 3

DSM - IV¹²⁾

158

97 , 61 1.6 : 1

10 13 (8.2%), 20 31 (19.6%), 30 55

(34.8%), 40 38(24.1%), 50 21 (13.3%)

37.1 ± 11.2

12.7 ± 8.5

D₂ 24.4 ± 9.2

2-6)

7)

2. 연구방법

1) 약물의 효과에 대한 평가

1 (Bromperidol, Chlorpromazine, Haloperidol, Nemonapride, Thioridazine, Trifluoperazine) 2 (Clozapine, Olanzapine, Quetiapine, Risperidone) (Chlorpromazine 400mg)¹³⁾ 4 가

(Treatment Response Scale : TRS)¹⁴⁾

Treatment Response Scale 가 1983 Csernansky 10 가

가 Brief Psychiatric Rating Scale(BPRS)¹⁵⁾

10 5 0 () 3 () 가 가 8 가

2) Genomic DNA의 정제

DNA Omega Bio - tek Inc.(P.O. Box 47310, Doraville GA 30362, USA) E.Z.N.A. Blood DNA Kit 500 μL 1ml cell lysis buffer(320mM sucrose, 1%(v/v) Triton X - 100, 5mM MgCl₂, 10mM Tris - Hcl(pH 7.6)) 가 5 10,000rpm 1 1ml cell lysis buffer 가 cell pellet , 250 μL phosphate - buffered saline(PBS) cell pellet , 250 μL PBS 가 cell pellet OB proteinase

(20mg/ml) 25 μL buffer BL 250 μL 가 vortex , 70 10 incubation vortex . 260 μL isopropanol 가 , HiBind DNA spin column 10,000rpm 1 DNA wash buffer(EtOH) 750 μL 가 10,000rpm . 13,000rpm 3 DNA elution buffer 150 μL 2 , 13,000rpm 1 DNA 1% (agarose gel)

3) 도파민 D₂ 수용체 유전자의 중합효소연쇄반응(Polymerase Chain Reaction : PCR)을 통한 증폭

D₂ (primer ; Bionics, Korea)

971(forward) : 5' - CCGTCGACGGCTGGCCAAGTTGTCTA - 3' 5014(backward) : 5' - CCGTCGACCCTTCCTGAGTGTCATCA - 3'

PCR 25mM MgCl₂, 200uM dNTP(dATP, dCTP, dGTP, dTTP), 0.5uM forward primer reverse primer . 25ng DNA, Taq polymerase(Bionics, Korea) 1unit 20 μL . PCR 94 4 (pre denaturation) , 94 1 (denaturation), 60 1 (annealing) , 72 1 30 (extension) 32 , 72 10 가 PCR 2 μL 2% agarose gel 100V 30 310bp

4) 증폭된 도파민 D₂ 유전자의 제한효소절편길이다형성(RFLP : Restriction Fragment Length Polymorphism)을 통한 분석

D₂

RFLP Taq I (Bio Basic Inc., Canada) 1U
 가 65 , 2% agarose gel
 () ethidium bromide
 (UV transillumination and
 autoradiography, Fotodyne Inc., New Berlin, WI
 USA) D₂
 Taq I site가 , 310base pair
 (bp) PCR 180bp 130bp
 Taq I

I(Bio Basic Inc.)

5' - T CG A - 3'
 3' - A GC T - 5'

3. 통계분석방법

T - Test,

SPSS 12.0 for Windows

결 과

1. 환자의 임상적 특성과 약물반응과의 관계

124
 73
 75 56
 , 가
 가 (1).

2. 도파민 D₂ 수용체 유전자 다형성

D₂
 Taq I 310bp, 180bp,
 130bp 가 . 310bp
 ,
 180bp 130bp
 (1). Taq I
 A1 , A2
 . 158 A1A1 22 ,

Table 1. Clinical characteristics of subjects

	Subjects on DRA(N=124)		Subjects on SDA(N=75)	
	R(N=73)	NR(N=51)	R(N=56)	NR(N=19)
Age(year)	35.1 ± 10.8	42.3 ± 11.0	27.2 ± 11.0	40.2 ± 11.2
Sex(M : F)	1.5 : 1	2.1 : 1	1.7 : 1	1.5 : 1
FHx(%)	14.7	12.9	18.3	13.3
DI(year)	11.9 ± 8.3	15.7 ± 8.6	9.1 ± 7.8	16.2 ± 8.2

DRA : Dopamine receptor antagonists, SRA : Serotonin-dopamine antagonists, R : Responders, NR : Non-responders, FHx : Family history, DI : Duration of illness

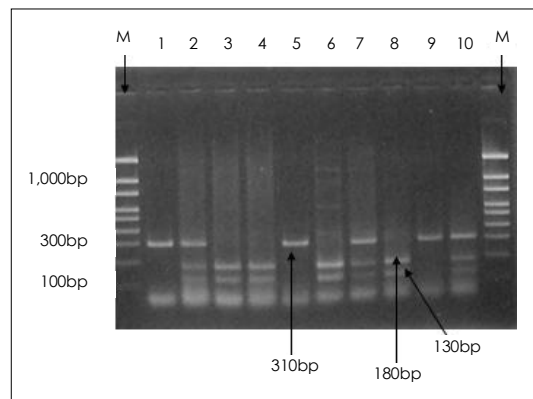


Fig. 1. PCR analysis of Taq I polymorphism in DRD₂ alleles from schizophrenic patients. M : 100bp ladder (marker), lane 1 : uncut(PCR product), A1A1 : lane 5, 9, A1A2 : lane 2, 7, 10, A2A2 : lane 3, 4, 6, 8.

A1A2 80 , A2A2 56 , A1A1
 13.9%, A1A2 50.6%, A2A2
 35.4% . Hardy -
 Weinberg (p=0.199). A1
 가 102 , A1 가
 56 A1 64.5%

3. 환자의 임상적 특성과 도파민 D₂ 수용체 유전자 다형성과의 연관

A1
 , 가 , A1
 (2).

Table 2. Relationship between clinical characteristics and *Taq I* A polymorphism of dopamine D₂ receptor gene

	Subjects(N=158)	
	With A1(N=102)	With no A1(N=56)
Age(year)	37.9 ± 10.9	36.3 ± 11.1
Sex(M : F)	1.7 : 1	1.7 : 1
FHx(%)	13.7	17.9
DI(year)	12.5 ± 8.3	12.9 ± 8.0

A1 : A1 allele, FHx : family history, DI : duration of illness

Table 3. Relationship between *Taq I* A polymorphism of dopamine D₂ receptor gene and response to dopamine receptor antagonists

	Subjects(N=124)	
	With A1*	With no A1
Responders	54	19
Non-responders	28	23

A1 : A1 allele, * : $\chi^2(1)=4.875, p=0.027$, two-tailed

Table 4. Relationship between *Taq I* A polymorphism of dopamine D₂ receptor gene and response to serotonin-dopamine antagonists

	Subjects(N=75)	
	With A1	With no A1
Responders	36	20
Non-responders	10	9

A1 : A1 allele

4. 약물의 반응과 도파민 D₂ 수용체 유전자 다형성과의 연관

가 (A1A1, A1A2)가 ($\chi^2(1)=4.875, p=0.027$, two-tailed, 3). A1 가

(4).

고 찰

16,17) 가 10) , , 18) 가 가 , 가 , 가 , 가 10) D₂ A1 A1 19-21) 가 가 22)23) D₂ Taq I A , A1 8)23)24) 8) D₂ 가 8)23)24) A1 가 가 D₂ 가 , 65~75% D₂ 가 , 24) Suzuki 10) nemonapride A1 가 , D₂ 가 A1 가 8)25)26) , A1 가 가 A1 가 10) Crow 27) 3H-D₂ Spiperone 가 가 D₂ 가

Taq I A
ment Response Scale

D₂
Treat-

가
가
가

Brief Psychiatric Rating Scale(BPRS)

10가

A1 가 TRS

가

D₂

가 가 A1

가

D₃,²⁸⁾ D₄²⁹⁾
2A,³⁰⁾ 2C,³¹⁾ 6³²⁾

중심 단어 :

D₂

Taq I

A1

D₂

참고문헌

가
158
83
34
41
(3) 2
(4)
가 가 가
10

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