

# 만성 정신분열병 환자에서 도파민 D3 수용체 다형성 및 혈장 Homovanillic Acid와 5-hydroxyindoleacetic Acid 농도의 치료반응과의 연관

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## The Association between Polymorphism of the Dopamine D3 Receptors and Concentrations of Plasma Homovanillic and 5-hydroxyindoleacetic Acid, and Therapeutic Response of Chronic Schizophrenic Patients

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### ABSTRACT

**Objectives** : Schizophrenia manifests a variety of interindividual differences in therapeutic response to antipsychotics. This might be attributable to dopamine and serotonin receptors that a important target for various antipsychotics, and the D<sub>3</sub> receptor(DRD3) alleles they carry. The purpose of our study was to investigate whether the plasma levels of homovanillic acid(HVA) and 5 - hydroxyindoleacetic acid(HIAA), and the polymorphism of DRD3 can be held as a predictor of treatment response in chronic schizophrenic patients.

**Methods** : Therapeutic response for 116 korean schizophrenia patient treated during 48 weeks were assessed by PANSS used as the clinical symptom rating scales. The levels of concentration of HVA and 5 - HIAA were examined by HPLC at baseline and at 48 weeks. We classified the polymorphism of DRD3 receptor using amplifying by polymerase chain reaction(PCR).

**Results** : Neither concentrations of HVA and 5 - HIAA nor genotype of dopamine 3 receptor were not significantly associated with the therapeutic response. But, the patients who has A1 alleles of DRD3 gene showed poor therapeutic responses.

**Conclusion** : A1 allele of DRD3 gene is associated with poor prognosis of chronic schizophrenia.

**KEY WORDS** : Schizophrenia · Dopamine D<sub>3</sub> receptor gene · Ser - 9 - Gly polymorphism · Homovanillic acid · 5 - Hydroxyindoleacetic acid.

## 서 론

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가 (Schmaus 1993) cl-  
 . ozapine D3 mRNA (Bu-  
 ckland 1993) , D3 가  
 가 가  
 (Socoloff , 1990).  
 가 D3 가  
 , , 가 Ser - 9 - Gly D3  
 , , homovanillic acid( HVA) 가 가  
 5 - hydroxyindoleacetic acid( HIAA)  
 가 . allele 2가  
 . 가 (Segman 1999, Lovlie 2000).  
 가  
 (Carlsson Lindquist 1963 ;  
 Anden 1970) 가 (Shaikh  
 , 1996, Rietschel 1996)  
 (Bleich 1988).  
 가 48 HVA 5 - HIAA  
 D3  
 HVA 5 - HIAA 가  
 (Davidson 1987 ; Stanly Mann  
 1983) 가  
 HVA 5 - HIAA  
 1 3  
 (Seeman 1992)  
 (Clair 1989 ; Sommer 1993 ; Su 1993 ; Wi-  
 ese 1993).  
 ,  
 DRD2 DRD4 Allele clozapine  
 (Mana 1998,  
 Peter 1994).  
 DRD3  
 . D3 가  
 (Socoloff 1992)  
 D3 mRNA

(Schmaus 1993) cl-  
 mRNA (Bu-  
 , D3 가  
 가 가  
 (Socoloff , 1990).  
 D3 가  
 Ser - 9 - Gly D3  
 가 가  
 allele 2가  
 가 (Segman 1999, Lovlie 2000).  
 가  
 (Shaikh  
 1996, Rietschel 1996)  
 .  
 가 48 HVA 5 - HIAA  
 D3

**연구대상 및 방법**

**1. 연구대상**

1998 4 1999 3  
 18 65  
 4 (DSM - )  
 116 . 가  
 ,  
 .  
 wash -  
 out period drug - free period 가 .

**2. 연구방법**

**1) 유전자형 분석**

(1) Genomic DNA  
 1.5ml 13,000rpm 1  
 , pellet ACE shocking solution(NH<sub>4</sub>Cl  
 8g, Na<sub>2</sub>EDTAH<sub>2</sub>O 1g, KH<sub>2</sub>PO<sub>4</sub> 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)

D3

5'GCTCTATCTCCAACCTCTCACA

3 '(sense) 5 'AAGTCTACTCACCTCCAGGTA3 '(an-  
 tisense)

10mM TRIS - HCl(pH 8.3), 50mM KCL,  
 0.2mM dNTPs, 20pmol primer, 1.5mM MgCl<sub>2</sub>, 3U *Taq*  
 polymerase 200ng template DNA 25ul

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

(3)

A1 A2 PCR Mlul  
 2% ethidium br-  
 omide (ultraviolet transill-  
 uminator) polaroid (polaroid, film 667)

## 2) 혈장 HVA 및 5 - HIAA 농도 측정

( ) 10cc EDTA - tube  
 - 70

3 5  
 HVA 5 - HIAA Seegal (1986)  
 (electrochemical det-  
 ector)가 high performance liquid chromatography  
 ( HPLC)

(1) HPLC : HPLC Waters (Waters Associ-  
 ates, Milford, MA, USA) model 510 pump, model 717

plus auto - sampler, Temperature control module(TCM)  
 Shiseido (Tokyo, Japan) model 2005 pulsed amperometric  
 detector(PAD)

Bus LAC/E card Millenium 2010 Chr-  
 omatography Manager software가 IBM PC  
 , column Shiseido (Tokyo, Japan)  
 250 × 4.6mm I.D., 5 μm particle size, reversed phase  
 C<sub>18</sub> column column temperature 30

(2)

sodium phosphate(dibasic), citric acid, isovanillic  
 acid, EDTA(ethylene diamine tetra - acetic acid, disodium  
 salt) Sigma (St. Lours, MO, USA), acetonitrile, tetrah-  
 ydrofuran Burdick and Jackson (Muskegon, MI, USA),  
 lyophilized serum Bio - Rad (Segrate Italy), perchloric  
 acid Wako Pure Chemical (Osaka, Japan), phosphoric  
 acid E. Merck (Darmstadt, Germany),  
 Milli - Q water system(Millipore Corp, Bedford, MA, USA)

3 Sigma  
 HVA 5 - HIAA , stock  
 lmg/ml - 70 가

(3) HVA 5 - HIAA : HVA

5 - HIAA perchloric acid  
 lml sample 4 , internal  
 standard 5 - Hydroxy - indole - 2 - carboxylic acid 100ng  
 vortex mixing , 50 μl perchloric acid  
 vortex mixing 30 4  
 13,000 × g 15

40 μl HPLC system

0.06M sodium phosphate(dibasic), 0.03M  
 citric acid, 0.0053mM EDTA가 phosphate buffer  
 945ml 50ml acetonitrile 5ml tetrahydrofuran  
 IL , pH 3.1  
 0.22 μm pore size filter ultrasonicator 30

1ml/min ,  
 PAD +800mV vs Ag/AgCl electrode  
 potential InA

HVA, 5 - HIAA  
 internal standard가 가 drug free  
 (ratio)

serum

3) 임상증상의 평가  
 Positive and Negative Syndrome Scale (PANSS) (Kay (1987))  
 PANSS 가 48 (39.03 ± 5.69, 39.60 ± 7.65), 가 22.53 ± 5.50, 22.60 ± 6.20  
 HVA 5-HIAA baseline  
 Independent t - test p-value 0.844, 0.805  
 paired sample t - test p - value 0.652

4) 통계분석  
 chi - square (a1a1, a1a2, a2a2) 47 (40.5%), 16 (13.8%), 65.9% 34.1%  
 HVA HIAA base line HVA HIAA t - test (2).  
 SPSS/PC+ version 10.0 0.05  
 DRD3 (3).  
 A1 allele 가 A2 allele 가

**결 과**

**고 찰**

126 10  
 116 ( 70 , 47 )  
 30 ( 18 , 12 )  
 86 ( 51 , 35 )

가

Table 1. Demographic data in chronic 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

HVA HIAA , DRD3  
 48

Table 2. Dopamine D3 Receptor genotype in chronic schizophrenic patients

DRD3 genotype			
A1A1 (%)	A1A2 (%)	A2A2 (%)	Total (%)
53(45.7)	47(40.5)	16(13.8)	116(100)

Table 3. Dopamine D3 receptor genotype and treatment response in chronic schizophrenic patients

Genotype	Responder	Non-responder	Total
a1a1	10(18.9%)	43(81.1%)	53(100%)
a1a2	13(27.7%)	34(72.3%)	47(100%)
a2a2	7(43.8%)	9(56.2%)	16(100%)
Total	30	86	116
Chi-square(p-value)	4.102(0.129)		
Allele			
a1	33(21.6%)	120(78.4%)	153(100%)
a2	27(34.2%)	52(65.8%)	79(100%)
Total	60	172	
Chi-square(p-value)	4.320(0.038)		

1, 가, DRD3, D3, Ser - 9 - Gly (Chia 1997), HVA, 133, HVA, D3, Ser - 9 - Gly genotype A1A1 (Shaikh 1996), allele 2가 genotype 2 - 2 (Putten 1989 ; Chang 1990 ; Mazure 1991 ; Davidson 1991), HVA, Davila 1988 ; Javaid 1990 (Picker 1990), (Ebstein 1997), 5 - HIAA, 가, A1 allele, allele 1 (Alfredsson Wiesel 1990), 5 - HIAA, BP- (Maziad 1997), A1A1 (Shaikh 1996), RS (1995), (Maziad 1997), A1A1 (Shaikh 1996), 가, 48, 1996 ; Sanober 1996), HVA, 5 - HIAA, 가, 가, 가, 가, HVA, 가, (Davidson 1987 ; Davila 1988), (Bo- wers 1989 ; Chang 1988), 5 - HIAA, 가, (Alfredsson Wiesel 1990), 가, 가, wash - out period, 가, 가, A1A1, allele 1, allele 1, 가, (Sanober 1996), 가, 가, A2A2, 가 50%, 가, 가, A2A2, (13.8%), 가, A1 allele, 가, (65.9%), HVA, HIAA, D3, DRD3

**결 론**

가

가

가

가

allele 1 가

가

가

가

가

D3

중심 단어 : D3 · Ser - 9 - Gly · HVA · 5 - H1AA.

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