

# 정신분열병 환자의 Tyrosine Hydroxylase 유전자 Intron 1의 VNTR 다형성\*

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## VNTR Polymorphism of Tyrosine Hydroxylase Gene Intron 1 in Schizophrenics\*

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### ABSTRACT

Until recently, the etiology of schizophrenia was generally attributed to abnormalities in dopaminergic neurotransmission. Specifically, an excess of dopaminergic activity in the mesolimbic system has been postulated to produce the positive symptoms, while decreased dopaminergic activity in the mesocortical system has been suggested to cause negative symptoms. Accordingly, we performed an association study of schizophrenia with TH gene.

Three hundred and seventy four biologically unrelated schizophrenic patients meeting DSM-IV-R criteria from Kangnam St. Mary's Hospital affiliated with Catholic university of Korea were recruited for our study. The 393 healthy controls were volunteers for DNA library of Kangnam St. Mary's Hospital without personal or family history of psychiatric and neurologic illness. DNA was extracted from peripheral mononuclear cells and polymorphic region was amplified by polymerase chain reaction. TH intron 1 VNTR polymorphism was typed by silver staining.

The allele distributions of TH gene were not different between schizophrenics and controls. However, the frequency of allele A was significantly higher in positive group than that of negative group of schizophrenics. These findings suggest that positive schizophrenia may be associated with allele A of TH gene.

**KEY WORDS** : Schizophrenia · Tyrosine hydroxylase · Genetics · Association.

### 서 론

정신분열병의 병인론에 있어서는, 일반적으로 도파민성 신경전달물질의 이상을 지적되어 왔으며, 특히 중뇌-전뇌 도파민성 신경전달물질의 과잉활동이 양성증상을, 반면에 전뇌-중뇌 도파민성 신경전달물질의 과소활동이 음성증상을 초래한다고 알려져 있다. 따라서, 우리는 정신분열병과 티로신 하이드록실라제(Tyrosine Hydroxylase, TH) 유전자의 변형성(VNTR)의 연관성을 연구하였다. 최근까지, 정신분열병의 병인론에 있어서는, 일반적으로 도파민성 신경전달물질의 이상을 지적되어 왔으며, 특히 중뇌-전뇌 도파민성 신경전달물질의 과잉활동이 양성증상을, 반면에 전뇌-중뇌 도파민성 신경전달물질의 과소활동이 음성증상을 초래한다고 알려져 있다. 따라서, 우리는 정신분열병과 티로신 하이드록실라제(Tyrosine Hydroxylase, TH) 유전자의 변형성(VNTR)의 연관성을 연구하였다.

1997

\*\*가

† : , 137 - 701 505  
) (02) 590 - 1533, ) (02) 594 - 3870

(Meltzer 1989)

가 , 가

(linkage study)

(association study)

(polygenic)

가 (Nothem 1993).

Tyrosine hydroxylase( TH) dopamine catecholamine (Nagatu 1964),

TPH 11 (11p15.5) (Craig 1986). Polymeropoulos (1991) TH intron 1

tetranucleotide(TCAT) variable number of tandem repeat( VNTR)

(TCAT)<sub>10</sub>/(TCAT)<sub>4</sub>CAT(TCAT)<sub>5</sub> turn-over (Wei 1997).

(Jonsson 1996 ;

Meloni 1997)가

TH intron 1 VNTR

가 ,

## 대상 및 방법

### 1. 대 상

가

-R(Diagnostic and Sta-

tistical Manual - R : American Psychiatric Association, 1987)

374

, 가

가

393

30.7 ± 9.7

32.2 ± 13.0

가

183 (48.9%),

191 (51.1%)

195 (49.6%),

198 (50.4%)

가

## 2. 방 법

### 1) 임상변인의 평가

가

(Positive and Negative Sy-

ndromes Scale, PANSS)(Kay 1987) . PANSS

가

가

(composite score)

가 1

, - 1

가 0

가

Brief Psychiatric Rating Scale( BPRS)(Overall Gorham 1962)

가

가

### 2) 검체의 채취 및 DNA 분리

( , )

10ml

Ficoll - Paque(Pharmacia, U.S.A.)

1 × 10<sup>6</sup> cells/ml가

0.5ml

pellet

0.5ml 가

50

60

90

10 가 - 20 (po-lymerase chain reaction, PCR)

× 10 PCR

(pH 8.0 100mM Tris -

HCl, 500mM KCl, 17mM MgCl<sub>2</sub>) 50 μl proteinase K(Boehringer Mannheim Biomedica, Germany) 0.07mg, Nondiet

P 40(Boehringer Mannheim Biomedica, Germany) 4.5 μl, Tween 20(Boehringer Mannheim Biomedica, Germany) 4.5

μl 가 0.5ml가

### 3) DNA의 중합효소 연쇄반응

TH intron 1 primers 5' - GCA AAA TTC AAA GGG TAT CTG G - 3' (sense), 5' - ACA GGG AAC ACA GAC TCC ATG - 3' (antisense)(Wei 1995)

100ng/ μl DNA 2 μl, 20 μM dNTP(Boehringer Mannheim Biomedica, Germany) 2 μl, × 10 PCR

(Boehringer Mannheim Biomedica, Germany) 0.1 μl

10 μl thermal cycler(9700, Perkin - Elmer, U.S.A.)

4) 유전자형의 판별

6% denaturing polyacrylamide gel  
 10% glacial acetic acid 30  
 3 3 0.  
 1% silver nitrate(AgNO<sub>3</sub>) 1.5l 37% formaldehyde 2.  
 25ml 가 30 3  
 3% sodium carbonate(Na<sub>2</sub>CO<sub>3</sub>)  
 1.5l 37% formaldehyde 2.25ml 1% sodium thiosulfate  
 300 μl 가 . Band가  
 가 . Size marker pUC19 se-  
 quencing ladder . TCAT  
 A<sub>p</sub>(130 bp) : (TCAT)<sub>10</sub>, A<sub>i</sub>(129 bp) : (TCAT)<sub>4</sub>  
 CAT(TCAT)<sub>5</sub>, B(126 bp) : (TCAT)<sub>9</sub>, C(122 bp) : (TCAT)<sub>8</sub>,  
 D(118 bp) : (TCAT)<sub>7</sub>, E(114 bp) : (TCAT)<sub>6</sub> 6가  
 ( 1), A<sub>p</sub> A<sub>i</sub>  
 sequencing ( 2).

5) 통계분석

chi - square test

student t - test

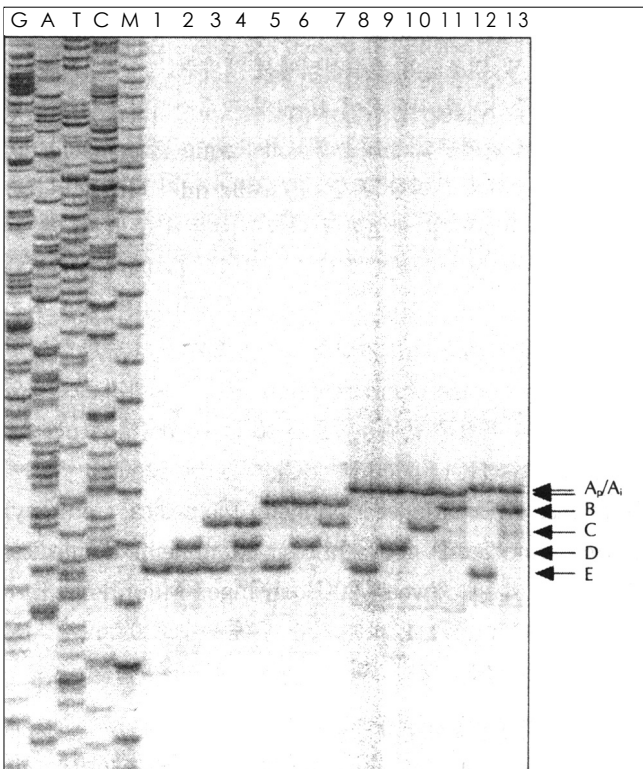


Fig. 1. Separation of PCR-amplified fragments of TH gene intron 1 allele by 6% denaturing polyacrylamide gel electrophoresis and silver staining analysis. Lane G, A, T, C : sequencing ladder of pUC19, Lane M : 30 - 330 bp AFLPTM DNA Ladder (GIBCOBRL, U.S.A.) increasing in length by 10 bp increments. A<sub>p</sub>/A<sub>i</sub> : (TCAT)<sub>10</sub>/(TCAT)<sub>4</sub>CAT(TCAT)<sub>5</sub>, B : (TCAT)<sub>9</sub>, C : (TCAT)<sub>8</sub>, D : (TCAT)<sub>7</sub>, E : (TCAT)<sub>6</sub>

=0.05

SP -

SS for Windows v7.5

결 과

1. 환자군과 대조군에서 TH 유전자의 분포

TH A<sub>p</sub>/A<sub>i</sub> : (TCAT)<sub>10</sub>/(TCAT)<sub>4</sub>  
 CAT(TCAT)<sub>5</sub>, B : (TCAT)<sub>9</sub>, C : (TCAT)<sub>8</sub>, D : (TCAT)<sub>7</sub>, E :  
 (TCAT)<sub>6</sub> 6가 가  
 (p=0.999) (p=0.999) Hardy - Weinberg  
 11/34(6.0%), 347(46.4%), 36(4.8%), 192(25.7%), 128  
 (17.1%) , 24/15(5.0%),  
 352(44.8%), 45(5.7%), 208(26.5%), 142(18.1%)  
 가 ( 1).

2. 환자군의 임상아형에 따른 TH 유전자의 분포

254 (67.9%), 89 (23.

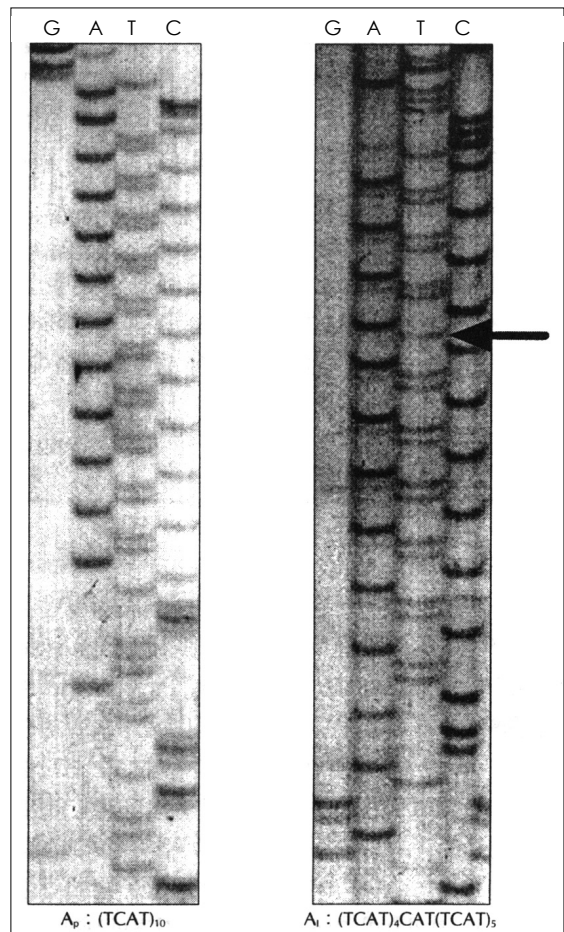


Fig. 2. Direct sequence gel comparison of the A<sub>p</sub> and A<sub>i</sub> allele. The T residue deleted was in A<sub>i</sub> that found in the fifth of the tetra repeat core motifs as indicated by the arrow.

**Table 1.** Allele distributions of THa gene in the subjects

|                        | Allele b (%)                   |             |           |             |             |
|------------------------|--------------------------------|-------------|-----------|-------------|-------------|
|                        | A <sub>p</sub> /A <sub>i</sub> | B           | C         | D           | E           |
| Schizophrenics (n=748) | 11/34 (6.0%)                   | 347 (46.4%) | 36 (4.8%) | 192 (25.7%) | 128 (17.1%) |
| Positive group (n=508) | 10/26 (8.8%) <sup>e</sup>      | 231 (32.1%) | 25 (6.1%) | 129 (31.6%) | 87 (21.3%)  |
| Negative group (n=178) | 0/5 (3.3%) <sup>e</sup>        | 85 (47.8%)  | 9 (5.0%)  | 50 (27.8%)  | 29 (16.1%)  |
| Mixed group (n=62)     | 1/3 (6.4%)                     | 31 (50.0%)  | 2 (3.2%)  | 13 (20.0%)  | 12 (19.4%)  |
| Controls (n=786)       | 15/24 (5.0%)                   | 352 (44.8%) | 45 (5.7%) | 208 (26.5%) | 142 (18.1%) |

<sup>a</sup>TH : tyrosine hydroxylase

<sup>b</sup>A<sub>p</sub>/A<sub>i</sub> : (TCAT)<sub>10</sub>/(TCAT)<sub>4</sub>CAT(TCAT)<sub>5</sub>

B : (TCAT)<sub>9</sub>

C : (TCAT)<sub>8</sub>

D : (TCAT)<sub>7</sub>

E : (TCAT)<sub>6</sub>

<sup>c</sup>Allele distributions between schizophrenics and controls were not significantly different

<sup>d</sup>Allele distributions between positive & negative groups were not significantly different

<sup>e</sup>  $\chi^2=4.292, p=0.038, df=1$ , for the comparison of the A<sub>p</sub>/A<sub>i</sub> allele versus the other allele between positive and negative groups

**Table 2.** Comparison of clinical variables according to the presence of allele A<sub>p</sub>(TCAT)<sub>10</sub>/A<sub>i</sub>(TCAT)<sub>4</sub>CAT(TCAT)<sub>5</sub>

|                                   | Allele A <sub>p</sub> /A <sub>i</sub> |             |
|-----------------------------------|---------------------------------------|-------------|
|                                   | +(n=44)                               | -(n=330)    |
| PANSS <sup>a</sup>                |                                       |             |
| Total score                       | 93.8 ± 13.6                           | 92.0 ± 13.4 |
| Positive score <sup>b</sup>       | 26.3 ± 4.2                            | 24.5 ± 4.9  |
| Negative score                    | 20.6 ± 4.6                            | 21.1 ± 5.0  |
| Change of BPRS <sup>c</sup> score | 12.0 ± 7.1                            | 12.2 ± 10.2 |
| Age at onset (year)               | 25.6 ± 8.2                            | 25.5 ± 7.6  |

<sup>a</sup>PANSS : positive and negative symptom scale for schizophrenia

<sup>b</sup>t=2.245 p=0.025

<sup>c</sup>BPRS : brief psychiatric rating scale

8%), 가 31 (8.3%)  
 TH A<sub>p</sub>/A<sub>i</sub> 10/26(8.8%),  
 B 231(32.1%), C 25(6.1%), D 129(31.6%), E 87(21.3%)  
 , 0/5(3.3%), 85(47.8%), 9(5.0%), 50  
 (27.8%), 29(16.1%) 가  
 , A<sub>p</sub>/A<sub>i</sub>  
 A<sub>p</sub>/A<sub>i</sub> 가  
 (p=0.038)( 1).

3. 임상변인

TH A<sub>p</sub>/A<sub>i</sub>  
 가 , BPRS , PANSS  
 A<sub>p</sub>/A<sub>i</sub>  
 (p=0.025)

( 2).

고 찰

TH 10 TCAT  
 A<sub>p</sub> : (TCAT)<sub>10</sub>, 10 T가

10 A<sub>i</sub> : (TCAT)<sub>4</sub>CAT(TCAT)<sub>5</sub>, B :  
 (TCAT)<sub>9</sub>, C : (TCAT)<sub>8</sub>, D : (TCAT)<sub>7</sub>, E : (TCAT)<sub>6</sub> 가  
 가 Puers (1993) 6가  
 (TCAT)<sub>11</sub> (TCAT)<sub>5</sub> 가 8가  
 , (TCAT)<sub>11</sub>  
 가 0.6%  
 가 Meloni (1995)  
 가  
 A<sub>p</sub> 가 1.5% 1.9%  
 가 Burgert  
 (1998) A<sub>p</sub> 가  
 가 Meloni  
 (1995) A<sub>p</sub> 가  
 Jonsson (1998)  
 A<sub>p</sub>  
 A<sub>p</sub> CSF homovanilic acid(  
 HVA), 3-methoxy-4-hydroxyphenylglycol( MHPG),  
 5-hydroxyindolacetic acid( 5-HIAA) 가  
 . Kidd  
 (1993) (association study)

Wei (1997) 227

A(A<sub>p</sub>/A<sub>i</sub>) 25

HVA 가 turnover

A가 turnover

TH



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